

**A Questionnaire Survey
on the Mathematical Model Sharing
in the Fields of Biosciences and Bioengineering
in Japan**

Physiome and Systems Biology Initiative Japan

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Introduction -Purpose of the Questionnaire Survey

The sequencing of the human genome was an epoch making event in reductionist life sciences, which liberated vast amounts of experimental data. Now, the challenge of the life sciences in the 21st century is to integrate this information into understanding of human physiology and pathology. In this context, advances in techniques for non-invasive measurement of human body functions, information technology, and the application of mathematics to nonlinear dynamical systems continue their remarkable development. The integration of these fields and techniques is moving the world towards a new generation of life science where physiological and pathological information from the living human body can be quantitatively described *in silico* across multiple scales of time and size and through diverse hierarchies of organization - from molecules to cells and organs to individuals. However, enormous amounts of information on human physiological functions accelerate a trend for physical and mathematical models of physiological functions to be detailed and complex with multiple degrees of freedom. Even when a model of a certain function is proposed and published in a peer-reviewed journal, it has been becoming difficult for most of third persons to reproduce the dynamics of the model and to reuse the model, which is obviously problematic. The “model sharing” concept has been proposed to solve this problem [1,2,3]. The model sharing concept aims to provide physical and mathematical models of biological functions for computer simulations (hereafter simply referred to as models) in a form that can be released via electronic media once the models are published in peer-review journals. The electronic media may be text files described in XML with enough meta-information to the extent that appropriate software can automatically produce a program source code which can be executed to reproduce the behaviors of the model shown in the publication. Alternative media may be just program source codes in common computer languages. These media guarantee the numerical-reproducibility of the models by any third party other than the scientist who has originally constructed, proposed, or developed the models. Thus the model sharing enables many researchers to reuse the published models, accelerating the promotion of sciences. This questionnaire is intended to survey awareness and opinion on the model sharing of individual scientists. Furthermore, we aim to make full use of the results of this survey to construct a model sharing platform on which information can be integrated and provided an opportunity to support the promotion of next-generation life sciences. Your cooperation will be greatly appreciated.

[1] [http://www.imagwiki.org/mediawiki/index.php?title=Model_Sharing_Strategies - One Day Mini-Workshop](http://www.imagwiki.org/mediawiki/index.php?title=Model_Sharing_Strategies_-_One_Day_Mini-Workshop)

[2] http://www.imagwiki.org/mediawiki/index.php?title=Minisymposium_planning

[3] http://www.imagwiki.org/mediawiki/index.php?title=Model_Sharing_Panel

Expected Respondent to the Survey

Researchers in the fields of

- Computational Biology
- Physiome
- Systems Biology
- Computational Biomechanics
- Computational Neuroscience
- Biological Engineering
- Biomedical Engineering
- Mathematical Biology
- Physiology
- Molecular Biology
- Neuroscience
- Cell Biology

Return Address and Reply Deadline

Return Address: admin@physiome.jp

Reply Deadline: July 23th, 2008

Policy for Usage of the Answer

The answer format includes your name. However, none of your answers will be made public with the name. This means that your answer may be posted on anonymously without your name. A summary of tally for each question may be made available to the public through the internet and academic journals. Since the model sharing concept could sometimes be directly associated with sharing and being available one's research bases and infrastructure, it would be naturally happen that you could not agree with the model sharing concept. Therefore, we will pay careful attention so that your negative answers, if any, will not cause any disadvantages for the respondent. With this understanding, we appreciate your ingenious answers to the questionnaires.

Questionnaires and Response Sheet

Name:

E-mail Address:

Affiliation:

Job Title:

Research Field of Expertise:

Note:

In the following of this summary, each question and its response (answer) are described in the same sheet. The questionnaire was distributed to 210 Japanese domestic researchers via email and we received the responses from 83 researchers. The following summary was based on these responses. Note also that the questionnaires and answers were performed in Japanese, and they were translated into English afterwards in order to make them available as public references. Moreover, most part of this summary has been reported in the IMAG and SIAM co-organized special Forward Looking panel discussion on the Future of Model Sharing in the 2008 SIAM conference on the Life Sciences. See

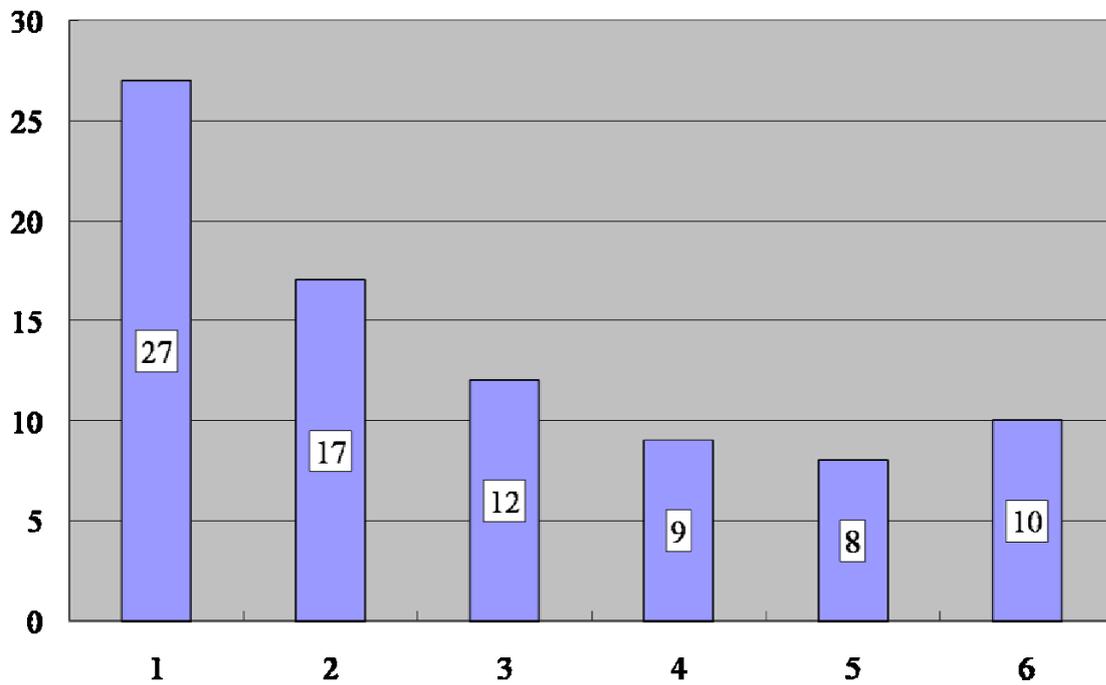
<http://www.siam.org/meetings/ls08/index.php>

and

http://www.imagwiki.org/mediawiki/index.php?title=Model_Sharing_Panel

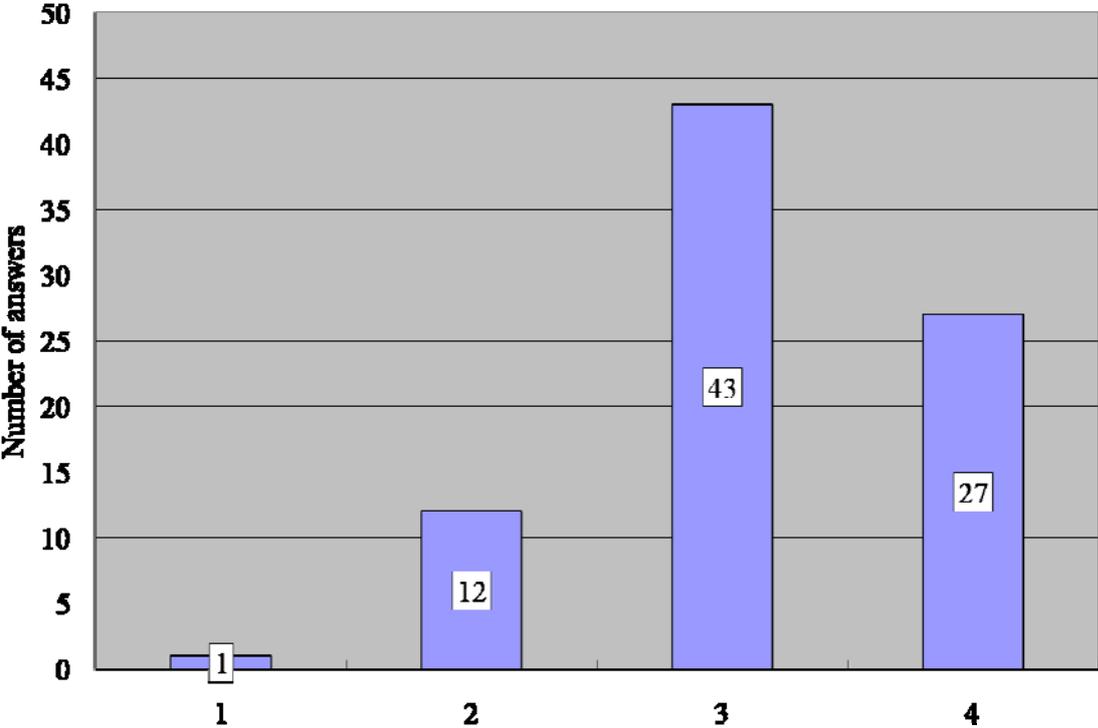
for more details.

Research Fields of Respondents



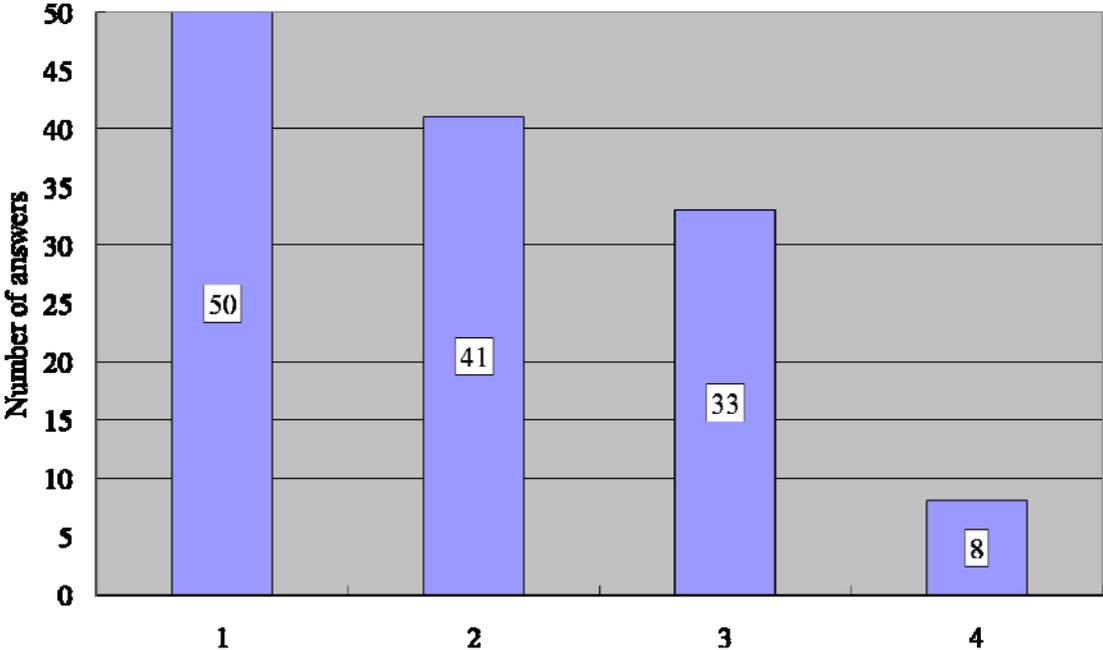
1. Biomedical Engineering
2. Physiology, Medical Sciences
3. Biomechanics
4. Bioinformatics, Systems Biology
5. Neuroscience, Neuroinformatics
6. Mathematical Biology and Others

(Q1) Select one as your attitude to Model Sharing Systems.



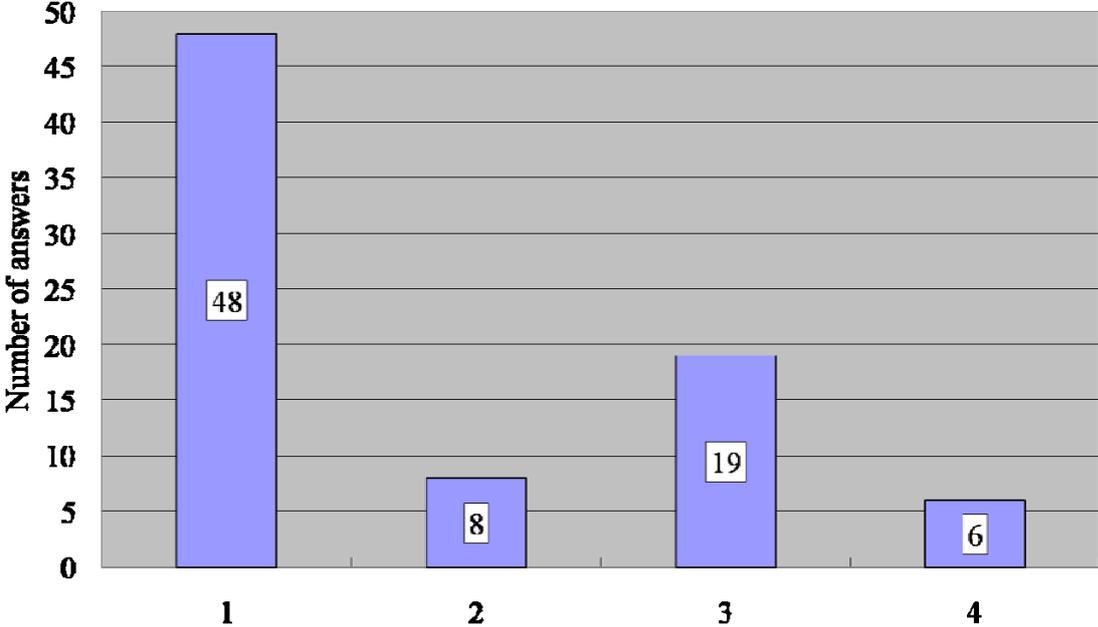
- 1. No interest and I will not use the system.
- 2. I will use the system but not contribute.
- 3. I will use the system and contribute.
- 4. I will actively use the system and contribute.

(Q1-2) Select one or more formats suitable for Model Sharing.



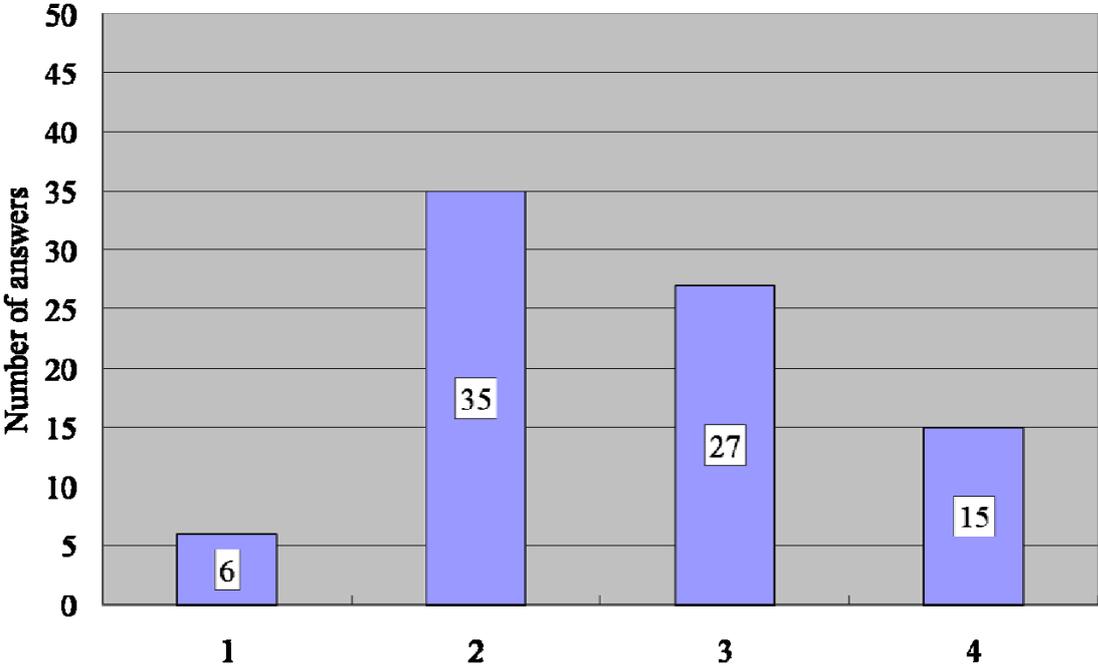
- 1. Model description formats for existing simulation software
- 2. Program source codes
- 3. XML-like model description formats with their interpreters
- 4. Others

(Q1-3) Select one organization suitable for constructing, supporting and maintaining a model sharing system such as model databases.



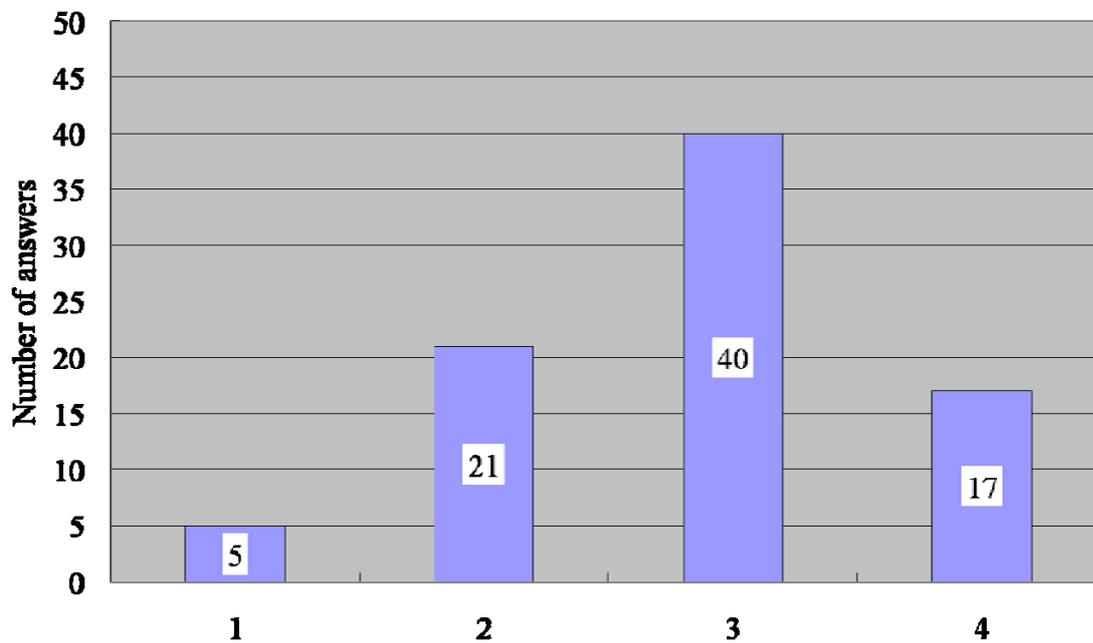
- 1. Academic society including NPO
- 2. Educational Institute/University
- 3. National Institute
- 4. Others

(Q2) Select an appropriate timing of your model publicity for sharing.



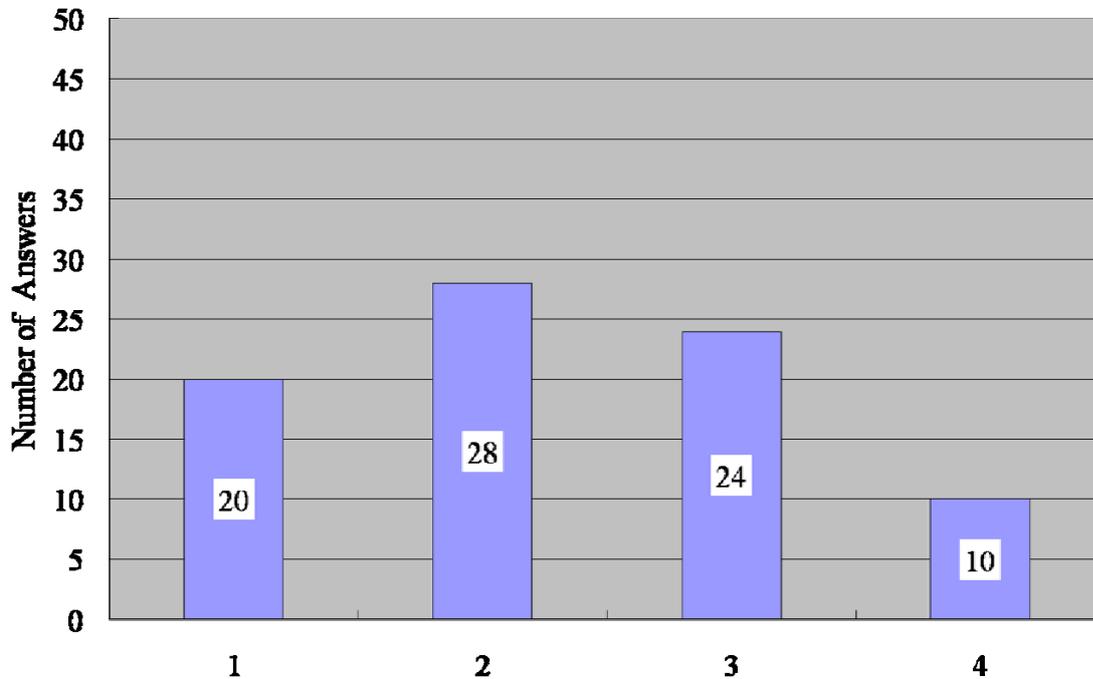
1. I will not share my model with others.
2. One or more year(s) after my paper publication.
3. Quickly after my paper publication.
4. Open for the referee and at the same time with my paper publication.

(Q3) Select one as your opinion for setting a model sharing policy by journal(s) in your field.



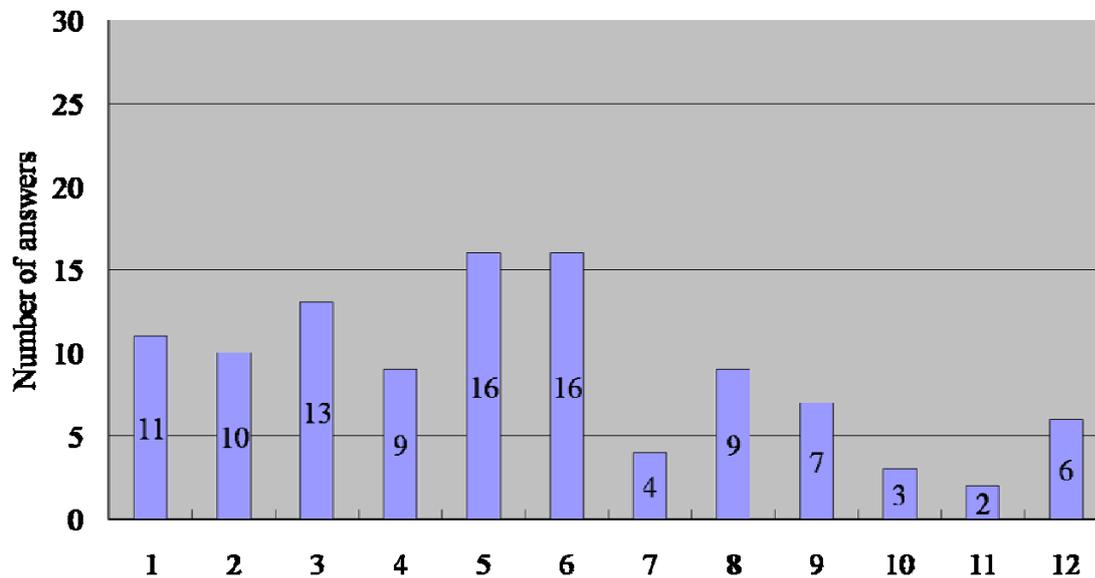
1. I will not agree and oppose such a policy.
2. I will not actively agree but accept for several journals.
3. Good for some journals to set such a policy for promotion of science.
4. Actively agree with such a policy for promotion of science.

(Q4) Select one closest to your opinion on the intellectual property of the model published in peer-review journals.



1. Intellectual property right of mathematical expressions of the model should be protected.
2. Mathematical expressions of the model do not possess an intellectual property right, but a program source code does regardless of its contents and it should be protected.
3. Mathematical expressions of the model do not possess an intellectual property right, but a program source code does if it includes particular (special) kind of algorithms. In such a case, an intellectual property right of the program code should be protected.
4. Mathematical expressions of the model and its simulation program code do not have to be protected of their intellectual property rights.

(Q5) Select one or more Model Sharing System(s) that you have been used or are planning to use.



1. BioModels.net (EMBL-EBI) Database <http://www.ebi.ac.uk/biomodels/>
2. e-cell SBML model repository <http://www.e-cell.org/ecell-models/repository/SBML>
3. CellML model repository <http://www.cellml.org/models>
4. NSR Physiome Models <http://physiome.org/Models/>
5. NEURON model database <http://senselab.med.yale.edu/modeldb/>
6. insilicoDB model database <http://www.physiome.jp>
7. INCF Japan Node Visiome <http://platform.visiome.neuroinf.jp/modules/xoonips/>
8. simBio <http://www.sim-bio.org/model/>
9. The Center for Cardiovascular Bioinformatics and Modeling <http://www.ccbm.jhu.edu/software/models.php>
10. National Resource for Cell Analysis and Modeling http://www.nrcam.uchc.edu/applications/published_models.html
11. SimBios <https://simtk.org/xml/index.xml>
12. Others

(Q6) Please provide your comments on the model sharing, public release of models, or related matters.

I think that the sharing of experimental data as well as the concept of model sharing have been widely discussed. From the viewpoint of model construction, it is natural for researchers to wish to use experimental data obtained under various experimental conditions in order to verify the validity and usefulness of the models. Based on my experience in providing my data to overseas researchers in response to such requests, the model sharing is necessary and useful as a method of joint collaborative researches. Such a trend has already become a reality in Neuroinformatics, Visiome, Physiome, and other fields. I take it for granted that the same attitude will spread also for the model construction and the model sharing.

In cases where I personally agree to the provision of experimental data or models, I can significantly contribute to the provision if I understand aims and purposes of the research of my counterpart (collaborator). However, if I imagine access to my model from unspecified general public, I actually feel hesitation to release my information to the public. It appears that, for the simulators currently open to the public (I am familiar with only Neuron and Genesis), their development itself is considered as the research. In this case, I think that the application to various cases and feedback of the results can provide useful information to the developers. On the contrary, a model that is published in a journal paper is often established in a manner that it operates only under specific conditions, in order to explain phenomena in which the paper's author is interested, not to open very details of the model. Therefore, communication with the general public obliged to the author should be limited.

I think it is necessary to construct a platform that can be utilized by researchers who release their models and experimental data at their will and try to actively use feedback on such information. A natural evolution of the concept of the model sharing will continue through the cooperation among researchers to establish related organizations, and those efforts will lead to the standardization. However, I do not think it is natural to accelerate the evolution of this concept by regulating and forcing the researchers to open their models as a precondition for publication in an academic journal. It is important to maintain the diversity of policies how one will conduct his/her research and publish the outcomes.

If the readers of a paper can reproduce or verify a model published in the paper, the model's reliability will increase, and it can be expected to accelerate the research promotion in the related fields. Therefore, I agree to the model sharing.

A process of submission of raw data used in the analysis of in a paper has been established in the field of brain function imaging. I understand that this is based on the same concept.

A comment on Q1-2:

In particular, in order to perform detailed and large scale simulations of human functions, it is inevitable to reuse models constructed by other researchers. The reuse of software has long been studied in the field of software engineering. Accordingly, I think that knowledge concerning conditions necessary for the resources to be reusable have been accumulated, in which a way to reuse models may be similar to the item 3 of Q1-2 in this survey; that is a general model description format. However, it is believed that currently there exists no well established way to reuse models where unique interpretation of arbitrary models has been verified using software engineering and techniques. If a large number of models are described in a current format, many of them may have defects in later years and thus they may require re-scripting again. In this context, I think it is necessary to urgently construct general description formats such as XML based standards, which are mutually convertible among several standards and are guaranteed their description capability, better than current specific XML based languages.

A comment on Q1-3:

For establishment of a common description format used as a standard, I think that the internet-related communication protocols and the accomplishment of standardization organizations for their description formats should be referred as useful examples. There exist various organizations such as IETF, W3C, and MPEG for such purposes. An organization providing a de facto standard is the one that has a strong leadership in its specific areas. However, considering that Japanese opinions have been hardly accepted by IETF and other organizations, a strong leadership is not always a good solution. Finally, I think all the situations heavily depend on the qualifications of the leader.

Making published models (program source codes) available in a form that they can be numerically reproduced is useful for the promotion of studies in the related fields. However, I think that it is essential to protect intellectual property rights.

Use of models only by individual researchers who have developed the models will slow down promotion of science and technology in the future. Therefore, making published models available for their reuse should be promoted. However issues of intellectual property right will become important because these issues are expected to be posed as a great obstacle to the model sharing.

Simulation models might be classified into two types. One is a model "without scientific novelty," which is intended to merely reproduce facts that has been proven already in clinical studies and biological experiments. The other type is a model "with scientific novelty," which is intended to shed light on unknown

physiological and pathological mechanisms and also facts that have not been clarified in biological and clinical experiments. These models may be used for discovering new drugs, creating a new industrial instrument, and to create intellectual properties leading to a new funding for competitive scientific researches. If the model sharing is going to be treated as an obligation of the researchers, I think it is necessary to differentiate between these two types of models. If it is made mandatory for researchers to openly release the latter type of models and their program source codes, they will hesitate to publish their academic outcomes, which could negatively affect promotion of the next-generation life science. On the other hand, it is desirable to make it mandatory for researchers to openly release the former model's source code, and it is strongly expected that the discovery and development of the second type of models with "scientific novelty" by the reuse of the former type public models.

Construction of platform systems for the model sharing and their operation obviously require an enormous amount of efforts. For this reason, I think it is better that such tasks should be performed by an organization with experts specialized for this issue.

Even if the model sharing is required at present, I think it is important to evaluate quantitatively requirements and expected results (outcomes) obtained after actual constructions of the model sharing system and also to establish platform systems that help experimental researches and promotion of their studies.

I think that models and simulation programs published in academic journals, in general, are considered as creative materials. Accordingly, their copyrights and intellectual property rights should be automatically generated. Considering burden of the authors necessary for releasing information about their model to the public as well as their intellectual property, it is difficult for the authors to accept a regulation of mandatory release (disclaiming the copyright as considered in Q4 of this survey) without any incentive and support for the release.

If an open source policy is really required for promotion of bioscience, I think that it must be conducted based on a researcher's voluntary release activities, not by regulations that enforce it by the academic journals. Such a voluntary activity can be seen, for example, in the Open Bio Foundation (OBF).

Mathematical expressions could be and should be released to the public. However if intellectual property rights concerning simulation programs of published models is not protected or alternatively equivalent incentives are not given to the authors and program developers of a published model, programming professionals in the fields of biosciences will not be encouraged, leading to the lack of excellent human resources of the fields.

I think we should develop a business model in which free software policy can be sustained in a long range. It is good to establish a mechanism in which incentive for the release of models and associated software is naturally generated by some fair evaluation of the effort made by the model author in a community.

I absolutely agree with the intention of the model sharing because I have had an experience working for the Visiome-project conducted by Dr. Usui at RIKEN. My impression of the project is that it is very difficult not only to construct a platform but also to update databases; it is also difficult to maintain a system without suitable ideas and schemes. Currently I am mainly involved in the molecular dynamics (MD) simulations. A large number of basic software (freeware) is available and used for the simulations in the field of MD simulations. Direct exchange of various software tools among researchers has become popular and usual in this field. These tools are extremely stable, useful, and user-friendly. I feel that the environment and situation around the use of NEURON and other similar software applications are becoming almost the same as MD community, although the number of users for NEURON is considerably small compared to that for the MD software.

Focusing on a simulator, or core software, it would be important to educate the users, i.e., how to use the software and its applications through seminars.

In the future, it will be ideal to standardize a model in a specific format; however, at the present circumstances, it is a waste of time for the user to describe a mathematical model using a specific format. In fact, I attempted to describe some models using certain formats such as SBML, but the conversion of the model to these formats bothered me. In some cases, such a format does not support a proper expression for the models. If models and programs such as FORTRAN, MATLAB, and other open simulators, which can be processed easily by a computer of the users, are available and their appropriate operations can be confirmed, they will be suitable at this first stage.

I agree to the concept of the model sharing in itself. However, the authors of the model might naturally want to keep some kind of advantages in the originality of the model. For this reason, I think that most of the authors might be negative or positive for the immediate release of details of the model and the program source code immediately after their paper publication. Moreover, with the model sharing system, reliability of the models will become critical. Sharing of any “incorrect” models could lead sciences to a wrong direction. An organization that verifies (curate) the adequacy of the shared models would be required before the release and during sharing of the models.

It is desirable to use any published models as freely as possible for the promotion of sciences. However, I cannot judge whether a model is being utilized absolutely

freely. This is partially because I am not familiar with this field. If simulation programs including models in any format can be executed using a computer, they can be considered as open software. Accordingly, discussions concerning open software license may be of problem.

The model sharing and public release of the models are critical in the sense that they basically create an environment in which any researchers can reproduce the simulated results of the models and that a further improvement of the model or constructing a new larger model can be efficiently performed by combining hierarchically the published models. However, it would be necessary to protect intellectual property rights so that any researcher does not face difficulties after his/her model publication. Furthermore, if a model is invented by a joint research project between researchers and a company, various measures for research evaluation may exist and they might be different for universities and companies. If publishing an outcome can be negative in terms of benefit of a company, a new model may not be published and released without an agreement with such companies.

I think that the following conditions will be required for continuous promotion of the model sharing in a sustainable manner.

-The model sharing and release should be recognized as an academic achievement and must be appreciated.

-It would be favorable to release a model independent of a journal paper publication. However, since it is important to assure the quality of the model, the model must be reviewed and edited in the same manner as done for peer review journals.

-The model release and continuous maintenance of databases should be performed by an organization that can permanently maintain them. I think that the National Institute of Informatics should maintain these databases in a consistent manner.

Names of contributors to the model sharing system should be acknowledged. The public announcement of researcher's name will increase his/her motivation, as is the case for publication in academic journals. I believe that the evaluation of researchers will evolve according to the following processes:

step 1. Paper publication

step 2. Patent

step 3. Algorithm

step 4. Intelligent chip

The model sharing will be useful to promote the first and 3rd steps. In any case, I hope this modeling system idea is actively promoted.

A platform for life sciences and bioengineering should be designed using only common information technologies as much as possible. Then only if there are any insufficient issues for which the existing methodologies are not capable of representing biology-specific knowledge, one would develop new techniques to overcome such insufficiencies. However, even in those cases, the bio-specific new technologies should be developed with a care so that they can be natural expansion of the existing non-bio-specific technologies and they can be somehow compatible with the existing non-bio-specific technologies in other fields.

In order to accelerate the promotion of the physiome related fields by means of the use of the open platform, appropriate mechanisms that can encourage and give some incentive by the user's contribution to sharing of his/her model. The assessment/evaluation of a public-shared model within a related academic community can play an important role as the same role played by the impact factors for the academic journal papers. Accordingly, the number of registered models for the model sharing will increase.

My research focuses on model simulations using realistic morphometric models of human tissues and organs to develop novel methodologies for qualitative clinical diagnoses. In my laboratory, we always try to have enough debates about computer simulations with the modeling experts and experimentalists. This is because experiments and computer simulations are "two wheels of one cart," and this is a policy of my laboratory for research and graduate student education.

However, there is a large gap between experimental scientists like me, who try to construct detailed models by extracting and approximating mechanical aspects of actual in vitro phenomena, and theoretical scientists who begin with generalized models and try to obtain biological interpretation based on the general principles of mechanics and computational models. Such a disagreement between two types of scientists always frustrates me. This would not be a problem if single researchers can perform both experiments and computer simulations, but this may not the case usually. It is desirable if there are some ways to reduce the distance between the two and to reduce the barrier between the two as much as possible. Actually, in my laboratory, experimental scientists only use "MATLAB" for their analyses of experimental data. Therefore, I would like to totally contribute to this concept of "Physical and Mathematical Model Sharing," since it will greatly help to integrate experiments, theories and computer simulations and to improve one's capability so that he/she can perform both experiment-based and computer simulation-based researches.

A procedure to make a model open in the public for the model sharing might be posing a heavier load on researchers in comparison with that required for registration of new genes into the gene data bank. Usually a model is developed by a scientist for his/her research, and its simulation code is often a kind of a spaghetti code with full of jargons. For this reason, it would be necessary for the scientist to rewrite the code so that it can be understood and utilized by others, to add and

improve comments in the code, to help and make instructions for the users, and to modify and update the code as needed. This requires enormous time and effort. Most scientists cannot find positive grounds for refining their model after completion of his/her study. For this reason, compulsory model releasing for the model sharing would bring about collecting models with low-quality only. I think that any incentive (e.g., model releasing and maintenance are recognized as one's achievement) is needed to make the model sharing systems valuable.

Some journals make it compulsory for the author to register their data of DNA microarray in the array databases when a paper dealing with the data is published. However, because some professional knowledge is required for such registrations, a large number of scientists hesitate to register their data. I suggest that a suitable organization that can control data registration and database maintenance, and can support scientists should be established.

Scientists working with animal experiments expect that computer simulation models can be used to complement disease-model animal. Even if genetic backgrounds of many mental disorders such as the integration disorder syndrome are identified to some extent, we are still in a state where we cannot obtain an appropriate model animal. If computer simulation models that are constructed with the aid of theories linking among hierarchies of genes to cells, tissues, organisms, and to individuals. This should deepen our understanding pathological conditions, and paves a new way useful for prevention and proper treatment/care.

A firm basis should be established before promoting the model sharing by considering how the intellectual property rights of the models are protected. This basis should contribute toward the development and promotion of the model sharing.

From the view point of patents, if the content of a patent becomes public via, for example, paper publication before its patent application, it becomes a common asset of the public and cannot be patented. In this respect, if a model is opened to the public without taking a patent right, it will not have intellectual property. Now, what will happen if a patent is applied for a model before it is publicized? In this case, I think that intellectual property rights should not be granted to mathematical expressions of the model. Otherwise, if the intellectual property right is granted to the mathematical expression of the model, any researcher should always pay a cost to the developers of the model for every use of the model, and no one can construct a new model based on the models whose intellectual property rights are protected, leading to a loss of fairness and harmful for promotion of science. This situation contradicts to the goal of common science. Apparently, this discussion does not imply that one does not have to respect the original or the pioneer work done by the authors of the model, and such a respect is usually expressed by citing the reference of the original work in a paper for the use of the

model and idea behind the modeling.

Regarding a program code simulating a model, allowing the free use the program code by others may be difficult for most scientists. In some sense, a program can be considered as a simple text by which the model's solution can be calculated by a computer. Hence, I think that intellectual property rights should not be granted to a program code based on the discussion above if the intellectual property rights are not given to the model. However, it might be very rare that the equations and simulation algorithms of a model are described so detail as to allow the third person to perform the same simulations shown in the paper. For complete reproduction of the simulation results, one should have technical know-how of the model and its simulation algorithm. Most researchers might be hesitating if the know-how for his/her model will become public by making his/her program code become public. Nevertheless, if we assume that the paper should include any know-how to allow third party reproduction and it is open to the public, it would also be appropriate to consider that both the model and its program code have no intellectual property rights.

For the model sharing to function effectively, I think it is necessary to establish a system that provides incentives to developers, for instance, as the patent system works. Although I think that operating a system in the same way as the patent system does not conform to the model sharing, I suggest, for instance, an idea to give an award to a developer of a model that is most widely reused. It could be a way of giving incentives to the developer of the model if companies are asked to pay a sort of license fee for their reuse the shared model.

Regarding the submission of the model to the journal referee in a way that the model's behaviors can be numerically examined for review purposes, I think there are no problems if such a review system can ensure the confidentiality of the model and can limit the use the model to confirm the validity of the paper.

Since the academic/scientific significance of the model sharing will increase, I think that it will be positively promoted in the future. However, it would be necessary to establish infrastructure that can protect several rights that the scientists provides models for sharing may have. In cases that a model are jointly developed with a profitable company may partially require to keep obligation of confidentiality, it is sometimes very difficult to open the entire model. Therefore, the model sharing must be flexible and be able to handle such circumstances.

Regarding the simulation environments that are targeted in Q1-2 of this survey, since the users of the simulation environments may not be limited to engineers, it is recommended that the environments should support formats for general-purpose simulation software such as Matlab and Mathematica, which allows the use of the environments by scientists from various, non-engineering fields.

I think that the model sharing would have its basis on disclosure of information. It would be preferable that scientists can provide or disclose useful information on their voluntary wills through various opportunities provided by academic societies and other organizations. In my opinion, a shared model with its program does not necessarily have one-to-one correspondence with a peer review journal publication. I do not think that a journal regulation obliging the authors to submit a program source code of a model proposed in their paper can largely promote and wide spread the model sharing concept. Moreover, the model sharing concept should not impose various restrictions on activities of researchers.

Regarding the development of model databases for the model sharing, it is desirable to perform research and development on the management of models/programs uploading system, such as integration of interfaces. It is recommended that a system enables us to use each model in the database as a module that can be easily reused to construct new models.

Bad money drives out good.

Collecting models haphazardly simply results in fomenting the reproduction of easy junk models. It might not be a rare case that execution of an advanced and valuable model requires very special circumstances. Execution time interval necessary for such models could be very long, say half a year to obtain simulation results.

Instead, the main focus of the model sharing should be targeting to provide “good models” as good references from which the researchers can learn many.

Such models and model-related data may be as follows:

- Reference models of molecular-molecular interactions
- References of kinetic parameters
- References of physiological parameters
- References of network topologies
- References for execution environments
- References of good mathematical models

In order to realize such a model sharing system, it is required to secure adequate human resources with high quality and enough number as “curators” and this point should be thoroughly considered. I really hope establishing the model sharing system such that an author of a model is admired when his/her model is registered in the model sharing system.

I've been involved in the development of free software. From my experience, in order for the model sharing concept to function, not only mathematical expressions of a model but also a program source code simulating a model (or source code of simulators if any) should be open to the public. However, only a few people can read the open source code and fix its bugs. I think that only a small group of core members can be deeply involved in the development of various types of free

software.

Concerning Q1-2 of this survey:

Does the item 1 assume MATLAB/SIMULINK? I think however it might not be appropriate to depend on commercial software. It is not favorable and convenient to use software with a lot of toolkits, since it poses cost and makes problems complicated, although the commercial software may be stable and easy to operate for general users and they are also good at detecting computational exceptions. Such software may have non-commercial compatible software, but in many cases such compatible software is not always maintained sufficiently.

Regarding the item 2 of Q1-2, I think that source code files is the most advantageous for the users in terms of their execution speed, but it might be difficult to use. If it is possible to use like numerical libraries such as LINPACK, it might be good.

Regarding the item 3 of Q1-2, it is difficult for me to determine whether the use of XML is appropriate as a language. I wonder who will assure the limitations and correctness of capability of simulators that read (parse and simulate XML based models) and how they are guaranteed. In this case, if the simulator's source code that is open to the public, this problem would be resolved. For researchers, the use of XML based model description is equivalent to learning a completely new language. For this reason, I think that a lot of samples and methods should be prepared so that the user scientists can easily achieve his/her description as they want. Simulators with interpreter-type appear to have a defect in terms of their execution speed.

I agree with promotion of the model sharing. However, I think it is appropriate to push for this concept after establishing rules concerning the handling of intellectual property rights of program source codes and other information. As indicated at the beginning of this questionnaire, the model sharing with program source codes directly relate to disclosure of research infrastructure. Accordingly, if the submission of a model is explicitly regulated as the rule for journal publication, it would cause confusion to the scientific community. In order to avoid any confusion, I hope the model sharing is promoted deliberately.

A wrong use of the model sharing system may involve a risk of plunging into "Number is Power," i.e., majority decision logic (the more users of a model, the more proper the model is). It is necessary to establish an educational environment and system to understand each shared model deeply and to ensure that it is correctly understood before its use.

I feel inclined to agree to the basic concept of the model sharing but I personally wish to link my model development to business opportunities if possible (although

currently my model may not be commercially used yet because it may be incompletely constructed). When it comes to business opportunities, I slightly hesitate to release my models to the public. However, for instance, open sources such as Linux can coexist well with commercial software in the software industry. I am not aware of details of the model sharing, but I hope that such a framework (coexistence of the model sharing and the commercialization) can be established.

I welcome the model sharing which may be able to evaluate research results in a reasonable manner. I think that a key issue to promote this concept is to consider how to protect the rights of model developers, although I cannot come up with a good idea. I think it is necessary to establish an appreciation on which to make a model publicly open is widely recognized as an academic achievement independent of publication of a paper dealing with the model.

I think it is also necessary to establish databases of experimental data to validate model simulations in parallel with or prior to the model sharing. It is necessary to establish a mechanism to collect experimental data required for simulations from these databases or to request data acquisition necessary for model simulation.

-Whether or not geometrical (morphological=shape) information should be included in a model to be shared must be separately discussed, since in that case, some other factors become problems such as availability of enormous computer resources necessary for reproduction of simulated behaviors of a model and ethical issues when patient data are used in a model.

-If any incentive for a model developer who may provide his/her model is explicitly defined, a spiral of intellectual activities will be formed as in the case of Science2.0. On the other hand, I feel hesitation to open my program source codes containing various types of know-how (they might be realistically too vivid), and I also imagine that there are many researchers who do not have sufficient time to make hand-compilation the code into an intermediate expression such as XML.

Finally, for young scientists who are forced to be more sensitive to their own short-term achievements and future positions rather than to the development and promotion of sciences, the ambitious perspective of "Model Sharing" may not be so attractive as expected.

-Promotion of model sharing

The concept of model sharing, model description using general-purpose extensible formats and releasing models into public domain might have been widely recognized among model-based researchers with engineering backgrounds because of their significance. However, this concept is less popular among scientists with medical biology backgrounds, in particular, experimental biologists who construct models in order to explain their "wet=in vivo and in vitro" experimental results.

Under such practical circumstances, I feel apprehensive that too rapid promotion of the model sharing may cause more separation between engineering and medical biology researchers. I think it is necessary to hear wide range of opinions from medical and biological scientists who are not deeply involved in simulation researches but are essential and primary to construct “good” biological models.

-Model description format

In relation to Q1-2 of this survey, it goes without saying that sharing of a model with a standardized format is desirable if such a description format with high description capability and versatility exists and becomes widespread. However, under present circumstances, I think it is most important that a model is released into the public domain in a way that any third person can reproduce a correct simulated behavior of the model regardless of its description format. For any model description format, it should be argued in its description capability and degree of its user-friendliness. In this sense, the format does not have to be an XML format. I think that the model description formats currently proposed are still immature and are not sufficient for widespread use, and thus at this moment, the researchers should not be enforced to use them.

-Model's intellectual property rights

I think that it is impossible to actually assert intellectual property rights for any mathematical expressions of models as in the case of general mathematical expressions and algorithms and they should not be accepted in the future. On the other hand, methodologies which have their bases on models of biological phenomena and are industrially effective with novelty and progressivity should be protected in their intellectual property rights. Intellectual property rights for such methods have been approved in many countries under current laws. Accordingly, there is no need to consider any additional and bio-specific rights for biological models.

In general, I agree with the idea that makes any model widely available to the public via electronic media. For this survey, I considered the model sharing concept based on a principle that "the continuous promotion of sciences with fair competition is effective to improve welfare of all mankind." Considering the current circumstances of modeling studies, I think it is effective for maintaining the above principle to review and validate all models within an open environment. Therefore, it will become important to form the open environment and to stably maintain it. In a case of failure of maintaining such an environment, it can happen that a model may be virtually monopolized by an accreditation organization that certifies the reliability and validity of the model. Such an exclusive right may adversely affect the model sharing concept in a short term range, and for instance, may be disadvantage for specific countries and organizations. However, in a long range, a certain equilibration of information and models would proceed and the model sharing concept will function better, and it will help creating an environment on which fair development of sciences is accelerated.

I am interested in two issues regarding the model sharing concept. One is about a model description language, and the other is about assessment (evaluation) criteria of modeling studies.

On the former, the user benefit may not always consistent with the benefit of the model providers. Both of them want to use a model written in own familiar languages. Therefore, I think that well-considered strict rules for model descriptions and language translation services will be required for practical use of the model sharing system. Moreover, we need to discuss who (the users or the model sharing system providers) bear the burdens. I am interested in the perspective or concept how such systems are going to be established.

For the latter issue, it is apparent that scientists cannot propose a new model in a short span of time and that the reusing a model requires less time than that required for a study proposing/constructing a new model. Although it is also important to apply an existing model to practical problems, it is more important to propose/construct a new good model. If a model sharing system enables releasing a model easily via an electronic medium, it is expected that a number of studies reusing shared models will increase. It is less desirable to bias research trend toward such a direction. I think it is necessary to establish a system that can fairly evaluate a scientist who proposes a good and valuable model. It may be a good idea to consider a model evaluation system based on the citation number as have been performed for journal papers.

If we assume that a certain source code has its intellectual property rights, I think it will be an important issue to consider how a counter value should be paid for the use of the source code. I can understand if a scientist who considers that it is good to release his/her models for the promotion of sciences but also who does not personally intend to open his/her model's source code to the public unless an appropriate counter value is guaranteed, and I believe that such intention should also be respected.

First it is impossible that an individual establishes a model sharing system and maintains/continuously operates it. It is desirable to find a public organization (or maybe private foundation) that shows the "understanding" for the model sharing system and its construction. Such an organization could offer financial support for a very long time. JST could be a candidate but they may be able to support the system only for a short period of time. Because the continuous operation of a system is indispensable, we are forced to seek volunteers from members of a specific academic society to operate the system on a continuous basis. However, to that end, importance of the model sharing concept and its system must be recognized by the society. Another requirement is that the field of "biological model simulations" should constantly generate achievements with high impact on the society and the economy that are equivalent or comparable to the achievements made by the field of life sciences. In addition, the field of biological simulations should provide profits or at least possibility of producing future profits. It would be

necessary to have a mechanism that enables autonomy as e-cell project has (had?). The protein structure database has been established. The same concept should also apply to models, model simulators, and their source codes, but issues of intellectual property rights should be involved.

Concerning Q4 of this survey, who will be the main organization that holds the intellectual property rights for parts or entire of the simulation and model sharing system? Will it be an academic society? How should we deal with the property rights of a developer or his/her organization/university? Can an academic society or organization freely say that “it is unnecessary to grant intellectual property rights to models and their program source codes?” Probably I think that intellectual property rights should not be granted to organizations such as academic societies. I think that the respondent has misunderstood the meaning of this question...

I encourage the active promotion of the model sharing and release for the development and promotion of science in this field. I think that we should respect not only opinions from people like a project manager but also from general scientists/engineers involved actually in developing software. Even if the model sharing concept can be supported by the project manager side, if the software developer and the scientist constructing a model have negative opinions about the release of the software, models and software cannot be always developed efficiently. Considering the loss of specialist personnel due to a negative effect of the model sharing and source code release, the model sharing concept may conversely hamper the development and promotion of biological sciences. When a scientist involved is employed for a specific project, they may be compelled to make a contract with the project manager under the condition that they agree to the software releasing into the public domain. However, they may not be always actively involved in the project. In such cases, they may move to other fields where they can play more important roles than in the field of biological sciences. Software is equivalent to an experimental device to conduct a scientific test but numerically by a scientist. A scientist usually values so much for his/her own test device. This is the same in the software engineer for his/her program source code. I think it is important to respect opinions of software developers and to obtain their consent for releasing the software into the public domain in order to allow a larger number of users to adopt better software. In this case, I think it is important to carry out the model sharing (source code releasing into the public) so that contributions of on-site software developers become well acknowledged.

Making details of published models available for the public is natural and proper for me. Without this, it becomes impossible to verify and validate published papers and the models therein. A model should be released into the public domain when a paper dealing with the model is published. This is also natural and proper if we imagine a journal paper on a discovery of a new gene which cannot be published without making the genetic sequence available for the public.

I think the model sharing and releasing models into the public are important for the promotion of science, but intellectual property rights should be protected. Unless we establish a system that can validate every model in published papers, it will pose an impediment of promotion of scientific. The number of biological models can explosively increase. In such a case, a system that can automatically validate published models will be required.