

Yoh Iwasa

Genomic Imprinting — Genes' Memory of Parents



Yoh Iwasa was born in Osaka in 1952. He studied Mathematics and Biology at Kyoto University, Japan. B.S. in 1975 and Ph.D. in Biophysics (Kyoto University) in 1980. After a short postdoc in Kyoto, he was a postdoctoral research affiliate at Stanford University, USA, 1981-1983, and a research associate at the Ecosystems Research Center, Cornell University, USA, 1983-1985. In 1985, he joined the Department of Biology, Kyushu University, Japan, as an Assistant Professor. From 1992, he has been a Professor of Theoretical Biology, Kyushu University, Japan. His research covers the modelling of diverse problems in biology, including spatially structured population dynamics, development (genomic conflict and pattern formation), the evolution of sex (genetic recombination, mating types, and sexual selection), and animal behavior. — Address: Department of Biology, Faculty of Science, Kyushu University, Fukuoka 812-81, Japan.

At the Wissenschaftskolleg zu Berlin, I have been given a rare and extremely important opportunity to concentrate on my research, freed from all obligations. The environment provided here was splendid. Especially with the help of the library, I was able to write a review article on the evolutionary theory of genomic imprinting, which covers fields I was not familiar with before. All the evolutionary biologists (Andrew Pomiankowski, Steve Frank and myself) have offices in the same building (Villa Jaffé), which was very helpful for our collaboration. Also, interaction with the insect vision group (Mandyam Srinivasan, Svetha Venkatesh, Hanspeter Mallot, and Roland Hengstenberg) has greatly stimulated my thought. Although we developed nothing concrete in terms of actual collaborative work progress, I am sure that this is a very important experience for my future work. I enjoyed Tuesday colloquia, despite the fact that most of the talks were far from my own field.

The year was very productive for me. In terms of output in the form of research papers that will be published in the coming years, my collaboration with Andrew Pomiankowski has been very important. We

succeeded in further developing the theory of sexual selection and identifying new aspects of genomic imprinting in mammals, which is also related to understanding brain function and human social behavior.

In the following, I will summarize the major work I have achieved during my stay at the Wissenschaftskolleg zu Berlin in year 1996/1997.

Genomic imprinting — Some genes remember whether they come from the father or from the mother, and behave differently. Why?

One of the hottest topics in the evolutionary biology is "genetic conflict". The genes of a single individual must cooperate with each other, and numerous genes of an individual are safely regarded as having a common interest. However, for some occasions, different genes show a different "interest". I studied one example of genetic conflict, namely genomic imprinting in mammals.

Most organisms inherit two sets of genes from their parents, and normally genes behave exactly the same way. However, recent molecular genetics has found that, in some mammalian genes, only the paternally derived copy is actively expressed, while the copy coming from the maternal side is inactive. These genes are typically those that are essential for the growth of the embryo, especially the development of the placenta, an organ designed to extract nutrients from the mother's body. Why is the paternal copy of the gene active and the maternal copy inactive? The genetic conflict theory notes that the paternal copy has a smaller chance of being shared by siblings (other embryos of the same mother) than the maternal copy if the mother accepts multiple mates in her life, and hence the paternal copy tends to be more aggressive in obtaining the mother's nutrients and care. I modelled this verbal argument into a formal genetic model in collaboration with my Japanese colleagues. The model supported the verbal argument — a growth enhancer evolves to show imprinting with the paternal copy expressed and the maternal copy inactive, while a growth suppressor gene tends to show an inactive paternal copy and active maternal copy.

In this year during my stay at the Wissenschaftskolleg zu Berlin, I examined the successes and failures of this argument in explaining the observed patterns of genomic imprinting. For example, there are several aspects of experimental results that are apparently in conflict with the hypothesis. I attempted to consider additional processes that may produce those deviations. By examining a series of models, I can show that

many of these apparent problems are explained by relatively minor modifications.

- 1) There are some genes affecting embryonic growth that are not imprinted (e.g. *Igf1*), which is a problem because a simple model predicts that all genes affecting embryo growth should evolve imprinting. This can be explained by considering recessive deleterious mutations in coding regions.
- 2) There is a gene that shows a pattern of imprinting that is perfectly reversed (*Mash2*). This gene is needed for placental growth and yet has an active maternal allele and an inactive paternal allele. This can be explained if the overproduction of this gene causes dose-sensitive abortion in early gestation.
- 3) Paternal disomies are sometimes smaller than the normal embryo. This is the likely outcome if imprinted genes control the allocation between placenta and embryo proper by modifying cell developmental fate.
- 4) For this reason, I concluded that the genetic conflict hypothesis is probably the correct explanation for the imprinting of autosomal genes (genes on normal chromosomes). However, I also identified a fourth problem:
- 5) Genes on X chromosomes do not follow the predictions of the genetic conflict hypothesis. For genes on X chromosomes, there are two additional forces of natural selection (sex differentiation; dosage compensation) possibly causing genomic imprinting in the opposite direction. Available evidence suggests that these processes are stronger than the natural selection caused by female multiple mating.

Finally the same formalism of evolution can handle an alternative non-conflict hypothesis — genomic imprinting might have evolved because it reduces the risk of the spontaneous development of a parthenogenetic embryo, causing serious risk to the mother's life. In contrast to criticisms given before, this hypothesis can also explain the major pattern of genomic imprinting.

These studies show that mathematical modelling of the evolutionary processes can make the logic much more clear than can verbal arguments. What is also very interesting is that the mathematical model for this genomic imprinting is in fact very similar, or mathematically almost identical, to the formalism Andrew Pomiankowski and I had developed for analyzing mate preference evolution (see below). It demonstrates one of the merits of mathematical modelling: that seemingly very

different subjects can be handled by the same analytical and conceptual techniques.

During my stay in Berlin, I have done all the calculations, and I have written up the main paper for the genomic imprinting evolution, a paper for imprinting for X-linked genes in collaboration with Andrew Pomiankowski, and a review article for the evolutionary theory of genomic imprinting. Without the great help provided by the library of the Wissenschaftskolleg, it would have been impossible for me to write a review article covering vastly different areas, including Obstetrics and Gynecology, with which I was not familiar before.

Sexual selection and mate preference evolution

The second field I have been working in the evolution of sexual ornaments and mate preference, in collaboration with Andrew Pomiankowski. Males often evolve an exaggerated trait, which can be an elongated tail, a very conspicuous plumage, or an elaborate song and dance. Some of these are used for male-male fighting. But in others (e.g. a peacock's tail), the females' mate preference is the prime reason for the male trait evolution, as demonstrated by experiments. Then we need to ask why female peacocks evolved mate preference for such an exaggerated trait. Why did females evolve to use tail length, instead of a long and elaborated song, as a criterion in her mate choice? To answer these questions requires mathematical modelling of the evolutionary processes.

There are basically two theoretical possibilities: The first possibility, called "Fisherian runaway", is that those male traits are simply fashionable. If females in the population have the propensity to be attracted to males with such traits (e.g. a long tail), choosing such males is beneficial for each female herself because she can produce sons with the same exaggerated trait and her sons will have a better chance of attracting females and achieving a high mating success. Mathematical models show that this process is likely to generate evolutionary cycles or perpetual changes — fashion. The second possibility, called "handicap", is that exaggerated male traits are indicators of male health or his quality as a mate. The female would benefit by mating with males of high quality, but quality cannot be seen easily. Long tails or elaborate songs are very costly to produce and hence only healthy males can afford to do so. Then females would be attracted to males who can do difficult jobs. This logic works only if these traits are really heavy and costly for the male — otherwise, even non-healthy males can produce the signal and

the female would not use it as a criterion for her mate preference. In the past, Andrew Pomiankowski and I developed mathematical genetic models and demonstrated that both of these processes are feasible.

At the Wissenschaftskolleg zu Berlin, we analyzed the cyclic evolution of multiple Fisherian traits. The mathematics is very similar to those used in the coupling of nonlinear oscillators in physics and engineering. We show that rapid speciation (formation of a number of new species) is possible based on this cyclic evolution of Fisherian traits and mate preferences.

Second, the handicap model has normally considered for the "good gene" process, in which a female chooses a male with a high genetic quality (stronger resistance to parasites, carrying fewer deleterious mutations, etc.). In this year, we developed a "good parent" process of a handicap model, in which females benefited directly by mating with a male of high quality who can help her in chick raising through his greater foraging skill, a better territory, etc.

By introducing a fast-slow de-coupling of the dynamics, we showed that the equilibrium female preference resulting from the good parent handicap has exactly the same form as with the good genes handicap. This allowed us to compare the relative importance of these two forces in the evolution of female preferences. The handicap model (both good genes and good parents) also shows cyclic evolution, as happens with the pure Fisherian model. However, since the handicap process is often strong enough to lead to a stable equilibrium, cyclic evolution is less likely to occur for handicap than for Fisherian traits.

We have completed both of these works and submitted them to journals. We also started a few other projects related to sexual selection.

With the support of the Wissenschaftskolleg, our group was able to host a workshop on the "Evolution of sex and genetic conflict" in mid-March. Most of the best theoreticians and experimentalists on these topics joined the workshop and the meeting was a memorable success. Every talk was exciting and discussion was intensive. Especially, Ichizo Kobayashi, of the University of Tokyo, proposed a new theory of the evolution of sexual reproduction, based on his molecular biological experiments using yeast, bacteria, and phage (virus parasites on bacteria). His work demonstrated the power and clarity of molecular genetic experiments using microbes compared to similar experiments using higher organisms (plants and animals). I feel that this area will make much progress in the coming years.

In June, the Innovationskolleg Theoretische Biologie, Humboldt University started, and the opening ceremony was memorable. In collaboration with the Innovationskolleg, the *Schwerpunkt* of theoretical biology

at the Wissenschaftskolleg will be able to develop an important world-wide center for theoretical biology.

Sexual difference in human behavior, and again genomic imprinting

Toward the end of the academic year, a new paper appeared in *Nature* on the socio-psychological behaviors of XO females (Turner syndrome). The individual with XO is more likely to cause trouble in social relationships if its X chromosome comes from the mother than if the X comes from the father. The straightforward interpretation is that a paternal X always goes to the daughter while the maternal X goes both to daughters and sons. Hence they are subject to different pressures of natural selection — a maternal X evolves to make boys causing more trouble and a paternal X makes daughters socially skillful. This is a clear example of genomic imprinting used as sexual differentiation. It is also clear that, for the genes on the X chromosome, the genetic conflict theory does not work. We developed the arguments for the difference of imprinting on X-linked genes and autosomal genes, and also plan to work on the modelling of X-chromosome imprinting evolution.

This gave me an opportunity to think about the relationship among evolutionary biology, the social sciences, and the humanities.

In the research report from last year, I found Rector Wolf Lepenies mentioning the "Streit der Biologen and der Geisteswissenschaftler". In this academic year 1996/1997 too, there was some tension between biologists, especially evolutionary biologists, and researchers in the humanities and social sciences. At the beginning of the year, I found some people hostile to biological, especially sociobiological arguments on human nature, or even to those on animal behaviors. Why do we use words so heavily culturally loaded, like mate preference, beauty, etc.? This is especially problematic if the issues are related to sexual differentiation, because "political correctness" is always involved. Instead of developing a serious meeting in which people from different fields and perspectives could come and discuss the issue, causing a confrontation between different branches of science, we decided to stay quiet and mind our own business, concentrating on writing books and papers, while interacting socially with all the people. In retrospect, this may have been a mistake we made this year. We could have done a better job by causing "confrontation", even if that would have taken some time from doing work in our own field.

In short, this year was extremely productive for me, in terms of the number of articles written and new perspectives in the field of evolutionary biology. It gave me an important opportunity to think about many aspects of evolution. I would like to thank the Wissenschaftskolleg zu Berlin and all the staff working there for this splendid opportunity.