Internal Conflicts and Organismal Adaptation: Mathematical Foundations

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Background

Multicellular organisms are held together by cooperation between their constituent parts: genes, genomes, and cells. This intimate integration underpins the complex adaptations that characterise plants, fungi, and animals. Like any collective, however, multicellular organisms are vulnerable to exploitation from within, whether by selfish genetic elements enhancing their own transmission at the expense of other genes or selfish cell lineages, such as cancerous tumours, diverting resources away from the organismal optimum. Internal conflicts arise because different constituent parts experience optimal fitness under mutually exclusive conditions.

While the presence of within-organism conflicts is well-established empirically, their implications for organismal adaptation are poorly worked out. The mathematical frameworks we currently use for optimization in biology—e.g., inclusive fitness, population genetics, quantitative genetics—generally assume that organisms are coherent, unified wholes, and they brush aside the existence of internal conflicts. Whereas the mathematics of cooperation has developed alongside its empirical study and has given rise to a coherent framework for understanding cooperation in various contexts, the mathematics of internal conflict has by and large lagged its empirical understanding and led to a proliferation of *ad hoc* models.

We convened this workshop because we believed that putting these topics—with all their various modelling approaches—together would yield two sorts of benefits: first, crosstalk between topics would spur progress and introduce new ways of thinking about old problems; second, a deeper appreciation of these topics as a coherent body of phenomena would emerge.

Participants

We hosted 38 scholars from four continents with affiliations in mathematics, biology, medicine, computer science, and philosophy. They included a mix of theoreticians and empiricists and were almost evenly split between junior and senior researchers. Here is a roster ([*link*]) of the participants.

Brief summary of activities

During the first day of our workshop, we had six tutorial talks that surveyed both the landscape of internal conflicts—i.e., selfish genetic elements to selfish cells—as well as the variety of modelling approaches—e.g., population genetic, quantitative genetic, and inclusive fitness models—that have been brought to bear on the subject. On the second day, we hosted 14 research talks and saw in greater detail how these conflicts are studied and how they have been modelled. On days 3 and 4 of the workshop, the sole activities were breakout discussions. These discussions proceeded organically, and by the close of the workshop, we had identified a number of avenues for future work, detailed below.

Tutorials

There were six tutorials on the first day. To start off, Manus Patten took us on a tour of the many forms that internal conflict can take. Next, we saw two talks on popular ways to mathematically model such conflicts. Maria Orive provided an outline of the Price equation and its multilevel decomposition, while Geoff Wild laid out the individual-centric inclusive fitness framework. After lunch, Hanna Kokko presented on how conflicts may affect population fitness. The day concluded with two talks, from Steve Frank and Jason Wolf, on how conflicts manifest in cancer and how they interact with genetic systems.

Research talks

1. Jake Scott: "Evolutionary therapy in cancer"
2. Manisha Munasinghe: "Transposable element-linked promoter structural variants are drivers of genome-wide differential expression"
3. Andy Gardner & Francisco Úbeda: "What is intragenomic conflict?"
4. Chuliang Song: "A theory of holobiont speciation"
5. Pavitra Muralidhar: "Cooperation within the genome promotes sex chromosome stability"
6. Tom Keaney: "Genomics of inbreeding avoidance/tolerance"
7. Tom Hitchcock: "Linkage generates conflicts within genomes"
8. Tom Scott: "No clear support for greenbeard genes"
9. Carl Veller: "Quantitative system drift"
10. Elizabeth Ostrowski: "The causes and consequences of microchimerism: A test of evolutionary theory in a wild carnivore population"
11. Abdel Halloway: "Ecological determinants of the evolution of sociality under parent–offspring conflict"
12. George Jarvis: "Conflict within cooperation: Macroevolutionary patterns in pregnancy and photosymbiosis"
13. Justin Blumenstiel: "Conflict with transposable elements as a catalyst for innovation" OR "Triggers of genomic autoimmunity by transposable elements"
14. Rob Unckless: "Single gene versus supergene meiotic drivers: When does the distinction matter in mathematical models?"

Discussions and future directions

After a day of somewhat free-form discussions, a number of future avenues for work crystallized. Here are a few:

- <u>Applications of game theory to cancer biology</u>
  Raja Panjwani, Jake Scott, Mati Patel, Tom Scott, Arvid Ågren

    - After some discussion, it was realized that Blackwell's Approachability Theorem from game theory might have applications in adaptive cancer therapy. Although these are seemingly unrelated topics, they both involve minimizing vector-valued costs over sequential choices. Scott introduced Panjwani to biophysics collaborators at Case Western Reserve, and together they have concluded that this project is worth pursuing. They will begin weekly meetings to work on this starting in October.
- <u>A model of parent-offspring conflict for mammals with alloparenting</u>
  George Jarvis, Andy Gardner, Geoff Wild, Francisco Úbeda, Dave Queller, Elizabeth Ostrowski, Jason Wolf
    - This group set out to turn ideas about alloparenting in mammals and the possibility for maternal-offspring conflict over direct maternal investment into a formal kin-selection model that could provide both clarity and testable predictions for comparative data. The group made substantial headway on the modelling during the workshop and have continued to work on the effort, bringing in additional collaborators (David Haig ad Cody McCoy). Currently, Jarvis is pulling together the relevant comparative data, and the group aims to have the model alongside the data ready for publication in 2027.
- <u>Evolutionary rescue meets internal conflicts</u>
  Rob Unckless, Maria Orive, Hanna Kokko, Abdel Halloway, Thomas Keaney, Julia Holder
    - The focus here is on how sex-ratio distortion is influenced by mating functions and how this all ties into ideas about evolutionary rescue. The group members have been meeting about once per month and have discussed a few different angles and challenges (e.g., the difficulty of comparing unlike study systems). They are still working through this and have really enjoyed chatting with each other during the follow-up meetings. Julia might be interested in modelling the mating function side of things.
- <u>A video series on modelling internal conflicts</u>
  Manus Patten, Manisha Munasinghe, and Mateus Lima
    - One idea that followed from the tutorials is that it might be nice to have more resources for the uninitiated, something to lower the barrier to entry into mathematical models of internal-conflict problems. The plan is to make a series of videos that offer a tight focus on papers that use different modelling approaches. The next step is to identify suitable papers. To be suitable means having a specific kind of modelling approach that is "teachable" and an author that is willing to walk through the steps of it, as well as the background and context, with us for our recordings.
- <u>Novelties</u>
  Justin Blumenstiel, Steve Frank, Nina Wedell
    - What is novelty in the context of intra-genomic conflict? This group discussed the importance of conflict for promoting novelty, or rather to enable 'escape' from this conflict. They found that the role of mutation rate, stochastic gene expression, and plasticity and the various times scales at which they operate were important considerations. Of particular interest is the potential of repurposing/ reusing existing traits/genes to generate novelty. In particular, the role of phenotypic plasticity and recombining existing genes in a new way was suggested to perhaps be a quick process to generate novelty/innovation more generally. One way to explore this suggestion would be to compare across systems with regards to internal conflict. Potential suitable systems could be cancer (immune costs/check points), microbial mechanisms that suppress overgrowth, the evolution of resistance/suppression, and public goods cheaters. A key aspect to consider is the time scale required to generate

novelty. Re-wiring and plasticity may be rapid (if heritable) versus mutation rate, which in turn vary across systems – e.g. high mutation rate at a short time scale in cancer. There is an ongoing discussion of whether the idea has enough legs to warrant a publication – perhaps as a short opinion piece somewhere, providing they can harness sufficient choice examples to illustrate their points.