# Task Group Summary 9

## *Can one control flow and transport in complex systems?*

### Challenge Summary

Transport in complex systems involves the flow of a quantity—information, power, mass, material, etc.—among the individual component elements. The nature of this transport depends both on the properties of the individual components and on the overall geometrical and topological structure of the system. In simple physical systems, we typically find either "ballistic" transport—that is, the distance travelled is proportional to time, as in the flight of a projectile—or "diffusive" transport—that is, the distance traveled is proportional to the square-root of time, as in Brownian motion describing the spread of a drop of dye in an unstirred liquid. In complex systems, as a consequence of inherent nonlinearities and complicated connectivity, transport becomes—no pun intended—much more complex. Two examples related to but distinct from standard diffusion will illustrate this complexity. Random walks in which the increments are distributed according to distributions with "fat tails" (instead of Gaussians) are known to produce "Lévy flights," in which interspersed with the small jumps typical of Brownian motion are long jumps that lead to "anomalous" (super-diffusive) transport. Such Lévy flights can occur in the spatial or temporal domain and are observed in analysis of data from earthquakes, finance, fluid flows, and animal foraging, among many other systems. When nonlinear effects—arising from predator-prey interactions or chemical reactions—are added to diffusion, the resulting "reaction-diffusion" equations can exhibit pattern-forming instabilities that can lead to "morphogenesis" or to wave-like transport with ballistic properties. A celebrated example is the model studied by Murray for the spread of a potential rabies epidemic in England. Murray showed that the underlying model (based on the Fisher equation) led to a narrow wave-front of contagion moving at a definite speed through the countryside.

When we consider complex systems involving networked structures, the problem becomes, technically, the study of transport on (arbitrary) graphs. Intuitively, it is clear that the nature of the network/graph—e.g., hub and spoke, long-range connections, random, etc.—will affect the transport dramatically.

Our attempt to understand the nature of transport in complex systems is in large part driven by the goal of controlling this transport. In some cases, we want to enhance transport: for instance, increasing the ability of the Internet to carry messages, enhancing traffic flow, increasing the rate of oil recovery or the efficiency of mixing and disseminating information in the case of a crisis, etc. In other cases, we want to inhibit transport—halting the spread of a virus or other contagion, preventing the collapse of an economic structure (the savings and loan sector, home mortgage sector), etc. *Apriori*, we can imagine controls that work on the components (nodes) of the system—e.g., changing interest rates or leverage requirements, vaccinating individuals—as well as controls that work on the connections (links)—changing diffusion constants, limiting travel, severing links. Overall, the challenge is to use these various controls to manage transport in a complex system so as to optimize it for a desired outcome.

To define this challenge more precisely, different task groups might consider one or more of the following four "case studies" from four very different disciplines.

1. In economic systems, the recent sub-prime mortgage fiasco represented "transport" by catastrophic cascading collapse; might it have been avoided if, in addition to interest rates, the

government controlled the "leverage" that firms could use? The infamous collapse in 1998 of Long Term Capital Management (LTCM), which failed due to margin calls, had its origin in an incorrect evaluation (by the world's experts!) of the actual risks involved in some of the investments; technically, their models failed to take account of the "fat tails" of the risk distribution. Can we create, before the fact, reliable models of risks in complex economic structures (or, what part of "derivatives" don't we understand)?

2. In oncology, we need to consider transport at both the molecular and organism levels. At the molecular level, cancer is usually a disease caused by mutations in genes important for cellular regulation such as cell cycle, development, apoptosis, etc. Although undeniably a good start, this description of cancer fails to explain fully the progression from quiescent, non-cancerous, to fully malignant and eventually metastatic cells and the accumulation of multiple cancer mutations along the way. Macromolecules such as proteins and RNAs encoded by cellular genes interact with each other to form a molecular dynamic system of great complexity. The systems properties of such molecular "interactome" networks have remained largely unknown until recently, primarily due to the lack of empirical description. In the aftermath of the human genome sequencing project, systems biologists are developing concepts, tools, and resources to model interactome networks with the goal of modeling differences of systems properties between cancerous and non-cancerous cellular networks. The ultimate goal of this endeavor is the design of drugs that would be able to alter systems properties of cancer cells to either kill them specifically or dramatically slow their malignant progression. At the organism level, we need to consider both how the primary tumor "transports" its malignancy—basically, by rapid localized (diffusive?) growth and displacement of normal cells—and how secondary tumors are created by metastasizing cells transported through the body by lymph or blood networks (Lévy flights?). Can we develop (perhaps different) appropriate therapies that will be needed to attack these two different forms of transport?

3. In public health systems, the challenges are both highly visible and daunting. Preventing the spread of various epidemics—SARS, Avian flu—and limiting the damage of the AIDS pandemic are among the most important problems facing society today. It is important to recognize that air travel—quite literally, a Lévy flight—played a significant role in the initial spread of AIDS between San Francisco and New York and the later studies that showed (*post-hoc*) that the spread of the SARS epidemic could have been predicted by air travel patterns, suggesting that restricting such travel in times and from regions of high contagion might be, despite its Draconian nature, an appropriate policy. Would this really be a workable and effective policy?

4. Much of our key societal infrastructure exists in the form of networks—the electrical power grid and the Internet are two important examples. The celebrated Northeast electrical blackout of 1965 was thought to have provided a transformative lesson, but a very similar cascading failure occurred in 2003 and likely could occur again. What lessons should we have learned from these failures? How can we control the system so as to keep the effects of power plant failures localized? Regarding the Internet, there are at least two key questions. First, the rapid spread of computer viruses with pandemic consequences is enabled by the Internet: can we develop a means of identifying these viruses as they travel and prevent them from attacking individual computers (i.e., severing the links)? Alternatively, the "mono-culture" of operating systems renders the individual computers much more susceptible to viral attacks: can we design operating systems that are sufficiently individualized so as resist these attacks (i.e., modify the nodes). Second, recent studies have shown that the Internet itself is particularly vulnerable to

attacks on its key hubs; how can we improve the systems to make it more resistant to these attacks? Clearly, both of these infrastructure “transport” issues overlap very strongly with the studies of robustness in other task groups.

## Key Questions

- In addition to the questions already posed in the individual case studies above, are there other overarching questions that we should consider?
- To what extent do the transport mechanism given in the examples above exhaust those likely to be found in complex systems? What can we add to this “taxonomy of transport”?
- Are there any universal aspects of transport in complex systems?
- What instructive “case study” examples can we find from other disciplines?
- What is the optimal mix of controls on the nodes versus controls on the links? How does this vary across different complex systems?
- How should we proceed to develop strategies to enhance desired flows and to inhibit undesired flows?

## Required Reading

*For Lévy Flights*

Geisel T, Nierwetberg J, and Zacherl A. Accelerated diffusion in Josephson junctions and related chaotic systems. *Phys Rev Lett* 1985;54:616-620. *For the Study of the Spread of Rabies in England*

Murray JD, Stanley EA, and Brown DL. On the spatial spread of rabies among foxes. *Proc Roy Soc (Lond)* 1986;B229:111-150.

Murray JD. Modeling the spread of rabies. *American Scientist* 1987;(May-June):280-284.

Solomon T, Weeks E, and Stanley H. Observations of anomalous diffusion and Lévy Flights in a two-dimensional rotating flow,” *Phys Rev* Lett 71, 3975-3979. [Accessed online July 31, 2008: [http://www.physics.emory.edu/~weeks/abs/nice95.html](http://www.physics.emory.edu/~weeks/abs/nice95.html).]

*For Cancer*

Huang S and Ingber DE. A non-genetic basis for cancer progression and metastasis: self organizing attractors in cell regulatory networks. *Breast Disease* 2007;26:27-54.

Kitano H. Cancer as a robust system: implications for anticancer therapy. *Nature Reviews Cancer* 2004;4(Mar):227-235.

*For Public Health and Epidemics*

Hufnagel L, Brockmann D, Geisel T. Forecast and control of epidemics in a globalized world. *Proc* Natl A*cad Sci USA*2004;101:15124-15129.

Severe Acute Respiratory Syndrome (SARS) background. Wikipedia reference. [Accessed online August 13, 2008: http://en.wikipedia.org/wiki/SARS.]

*For Economic “Collapsing Cascades”*

Long-Term Capital Management. Wikipedia reference. [Accessed online August 13, 2008: http://en.wikipedia.org/wiki/LongTerm_Capital_Management.]

Report of the CRMPG III August 6, 2008 (Counterparty Risk Management Policy Group III). Containing systemic risk: the road to reform.[Accessed online August 13, 2008: http://www.crmpolicygroup.org.]

*For Power Grid Failures*

Kinney R, Crucitti P, Albert R, Latora V. Modeling cascading failures in the North American power grid. *Eur Phys J* 2005;B46:101-107.

## Suggested Reading

Barabási AL. The day the lights went out; we're all on the grid together. *New York Times* 2008. Opinion. [Accessed online August 13, 2008: http://query.nytimes.com/gst/fullpage.html?res=950CE5D91430F935A2575BC0A9659C8B63&scp=9&sq=barabasi&st=cse.]

Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *The Lancet* 1996;437:1312-1314.

Källén A, Acuri P, and Murray JD. A simple model for the spatial spread of rabies. *J Theor Bio* 1985;116:377-393. Lengvel I and Epstein IR. A chemical approach to designing Turing patterns in reaction diffusion systems. *Proc* N*atl* A*cad Sci US*A1992;89:3977-3979.

Levine H and Rappel WJ. Membrane bound Turing patterns. *Phys Rev E* 2005;72:061912.

Mandelbrot B. *The Fractal Geometry of* N*ature*. W.H. Freeman and Company 1982.

Murray JD and Seward WL. On the spatial spread of rabies among foxes with immunity. *J Theor Biol* 1992;156:327-348.

Turing AM. The chemical basis of morphogenesis. *Philosophical Transactions of the Royal Society B (London)* 1952;237:37-72.

Due to the popularity of this topic, two groups explored this subject. Please be sure to review the other write-up.

## TASK GROUP MEMBERS – GROUP B

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# TASK GROUP SUMMARY – GROUP B

*By Brian Creech, Graduate Science Writing Student, University of Georgia*

Charged with the problem of how to control transport in complex systems, a group of scientists at the 2008 National Academies Keck *Futures Initiative* Conference on Complex Systems agreed that a control mechanism should be simple, impacting transport while also presenting the fewest negative effects on the health of that system. In Task Group (9B) two of the questions that arose are if there exists a single factor that affects the flow of a quantity across an entire system, and whether a system remains complex if it can be altered by a single variable.

The answer to the first question is yes: temperature. In several different systems, from the human body to deep sea ecologies, slight changes in temperature set off a complex series of reactions that change how things move across the system. The complexity of these systems amplifies small temperature changes across the entire network, resulting in the slowdown or cessation of entire processes in a series of chain reactions that affect the state of the system. A simple change in temperature can have damaging and irreversible consequences on the structure of the system. Taking the earth as an example of a complex system, global warming is a change in temperature across the entire system. A rise in temperature may increase the likelihood that non-native flora and fauna survive in polar regions. Temperature rises may lead to the development of new and sometimes catastrophic weather patterns, ocean levels rise, and animal and plant species die off due to a chain of events instigated by a subtle change in temperature.

One representation of a complex system is an (arbitrary) graph where transport of the quantity of interest—information, material, mass, energy—occurs over the nodes and links. Identifying optimal control points requires knowledge of the set of nodes and edges, the topology of the graph.

The group considered a “dynamic network model” of a complex system where nodes and edges appear and disappear over time. A node may itself represent a network at a lower level, in much the same way that network representations of organ systems can be viewed as subnetworks of a network representation of the organisms as a whole. When conditions change within organs and tissues, the conditions of transport across the entire body are changed.

The Task Group started to formulate dynamic network models of the spread of HIV/AIDS and cancer metastases. The human HIV/AIDS pandemic was viewed as a disease transported across a network where nodes correspond to individuals; cities are a series of dynamic nodes connected by airlines, with the disease being transported via the changing social/sexual connections among infected and non-infected individuals within the cities. Metastatic cancer was modeled as a network within the human body that uses the lymphatic system and the venous system to transport cancer from one organ to the next. The body’s organs are themselves dynamic networks, and are subject to the same characteristics of a larger dynamic network. Both examples have important similarities, but their differences impact how diseases move across the networks.

## Spread of HIV/AIDS Among Human Populations

The most notable difference between the spread of metastatic cancer and the spread of HIV/AIDS is the dynamic nature of the links in the HIV/AIDS network. Personal habits change; people quit using drugs or start using drugs, and old sexual connections fade while new ones are forged.

The spread of HIV exhibits the “birds of a feather flock together” phenomenon, where individuals within certain subcultures and socioeconomic groups are more likely to contract and spread HIV. Although effective methods for slowing down or inhibiting the spread of HIV/AIDS such as increasing the use contraceptives are known, personal habits and behaviors often confound such control methods. For example, lifestyle choices are highly individualized and notoriously hard to control, but education before the fact is less draconian than widespread quarantine afterwards. Thus, one good control mechanism is localized education campaigns that change the habits of enough individuals so that the disease becomes localized within smaller and smaller groups. Prevalent cultural attitudes, education level, and income all play a role in an individual’s ability to be influenced by knowledge about how AIDS is spread, making education the most expensive and complicated means of control. Models that measure control need to account for these differences and reflect how effective certain types of education are among different groups of people, while also identifying the more mobile and connected groups that are more likely to spread the disease throughout the wider population.

## Metastatic Cancer Spread

Cancer cells and cytokines, the molecules used in cellular communication, can move through the body via the lymphatic system, a system that closely resembles the network of train tracks within the United States. The key to finding a control mechanism to slow or stop the spread of cancer is to look for the most effective roadblocks for the system, and then find the heaviest traveled paths on which to place these roadblocks. This model looks at metastases—the spread of cancer cells to new parts of the body, for example malignant breast cancer cells moving to the bones—as a structural phenomenon. The body’s immune system offers a means of implementing control. A model of metastatic cancer spread could be used to test how specific manipulations of the immune system might impede or encourage the growth of cancer as well as their impact on other parts of the body. In cancer patients, original tumors are often not the most dangerous; rather tumors that metastasize prove to be more deadly and less amenable to treatment. Elderly cancer patients tend to die of something other than cancer and show fewer signs of metastases.

It is important to remember that not much is known about the mechanisms that influence the spread of metastatic cancer. What is primarily needed are the data to help build a network architecture that matches ob served patterns of the spread of metastatic cancer. Instruments or methods are needed to measure flow between the lymph nodes and organs. Endoscopic imaging techniques have been used to observe cancer cells in the gastrointestinal tract and may provide the necessary means of tracking the mechanism for metastatic spread.

## Conclusions

The unique features of individual networks affect the patterns of flow within that network. In the case of metastatic cancer, there is evidence that cancer spreads from lymph node to lymph node. A fruitful territory to explore would be a model that mimics metastatic spread along the lymphatic system.

At this point, the key is to determine factors that impact flow across the network. By modeling metastatic cancer spread along the lymphatic system, it may be possible to learn how cancerous cells and cytokines move across the system, whether through a series of Lévy flights—random, long-range jumps into a new environment—or by diffusing across the system, signaling tumor growth within hospitable organs.

The question remains though, can a system still be complex if it is impacted by change in a single variable? A network's complexity amplifies change in the single variable across the entire system, but the consequences of that amplification can be damaging. One hopes that for metastases, simple roadblocks are found and that the solution is something as simple as changing the temperature of the body. As shown with the spread of HIV/AIDS, though, simple, wide ranging solutions, like draconian quarantines, can also limit the flow of benficient material across the entire system. Like education strategies geared towards local culture to prevent the spread of HIV/AIDS, what is needed to control metastatic spread is a mechanism that can be implemented locally, without affecting the healthy flow for the rest of the body. The relative simplicity or complexity of that solution remains to be seen.