John Vastola

9/21/18

**Response to landscape outline comments**

**Comment on intro:**

“I would think about this as the history of the landscape idea from Waddingtons time to more recent times.”

**Response:** You bring up an interesting issue: should we present things from a historical point of view or a pedagogical point of view? My preference is for a more pedagogical point of view.

Subjects that are better understood (or that are on the verge of it) are generally presented from a pedagogical point of view; for example, lots of more recent quantum mechanics textbooks go straight into the formalism, and talk about Schrodinger’s equation and how to solve it, without first recounting the photoelectric effect, or the Stern-Gerlach experiment, or weird atomic spectra results. Lots of older quantum mechanics books spend time on all these things before getting into the formalism, to the detriment of the modern reader trying to quickly learn and apply quantum mechanics.

We have an opportunity here to be among the first people to give a ‘coherent’ point of view on landscapes—and so I think taking a historical point of view would be missing this opportunity.

**Comment:**

I said: “Begin by (briefly) explaining Waddington’s epigenetic landscape metaphor: a cell is like a ball rolling around in a rugged landscape, until it eventually settles down in a valley/stable cell type. Don’t dwell on this too much, since it’s been explained in exhaustive detail elsewhere.”

You said: “I think there is some subtlety here to get into at some point. I’ve never much liked this ball rolling down a hill idea. At the level that we usually think about landscapes, the landscape itself is not a fixed construct. Rather, as parameters change (over time), the landscape itself evolves and changes. Now, of course if you go to a lower level where those parameters are controlled by other variables, then you can think a bit more like that rolling down a hill idea. However, that is not usually the context that landscapes come up in.

I think these distinctions are important to discuss, particularly for the non-expert audience.

In particular, I think it is in important to talk about what determines the structure of a landscape as well as what alters a landscape. Alternatively, discuss transitions within a fixed landscape versus transitions that occur due the changes in the landscape.”

**Response:** This is a good point. I agree.

**Comment: (on What is the landscape?)**

“Here I would talk about the issue of what shapes a landscape versus what changes a landscape. Also, discuss the different levels at which a landscape can be thought of. The idea, that if you go to a lower level of biology, parameters become variable dependent and so forth.”

**Response:** Good idea.

**Comment: (on The landscape in practice)**

“Your bullets don’t match the title to me. Here, rather than talking about the limitations and issues (those should come later), I would talk about the use cases. Visualizing a models state space. Relative stability of states. Transition paths. Etc.”

**Response**: I figure that the technical things a landscape can give you (relative stability, transition paths) should be discussed in the next section, especially since the point must be made that one cannot get each of those things together using the same landscape.

Here, I mainly just wanted to remind the reminder (before we get into the weeds) that the landscape concept has still got plenty of kinks that need to be worked out before it can be of more general purpose use. There is already a meatier section devoted to discussing this in some detail later in the paper, but I think it’s worth mentioning up front too.

Maybe this does not need a subheading; it can just be a short paragraph tacked on to the end of the intro.

**Comment: (on GENERIC PROPERTIES OF THE LANDSCAPE)**

“I think all the material in here is good, but that most of it should either become higher level “intro” material or be made a lead in to the main landscape methods section.”

**Response:** One of the nice things we can do with this paper is offer a more precise notion of what a landscape is and what it can do for you. I think it would be nice to explore those sorts of subtleties in their own section, so that the reader is primed for understanding the strengths and limitations of each of the concrete landscape constructions we discuss. For example, they should keep in mind in advance that global stability information is generally incompatible with local transition information.

Actually, what I would really like with a section like this is to offer a mathematically precise (or at least reasonably precise) definition of a landscape at the end of this section, motivated by some discussion of what properties we want landscapes to have. Then we can mention how each specific landscape construction we discuss satisfies those properties.

In particular, it would be good to define “local landscapes” and “global landscapes” or something like that.

**Comment: (on The landscape for equilibrium systems)**

“I would make this the first section of the “Different Landscapes” section. In some sense, this is an intro to the idea that serves two purposes. Motivate the basic idea. Explain why this doesn’t work for non-equlibrium systems.”

**Response:** Maybe it could fit at the beginning of “Different Landscapes”. But I wanted to mention something about landscapes for equilibrium systems here so that it is clear what kind of properties we are trying to generalize (i.e. regarding attractor stability and transition rates). Something should be mentioned to that effect here, including why there are issues with this for non-equilibrium systems, like you say.

**Comment: (on The landscape for equilibrium systems)**

“I think this is the right spot.”

**Response:** See above response. Probably some discussion could go both here and in “Different Landscapes”.

**Comment: (on Modeling a generic biological system)**

“This gets at a point I was discussing in above comments. I would talk about this more at a qualitative level rather than a thermodynamic level.”

**Response:** I agree. It’s probably worth mentioning in the intro too.

**Comment: (on Properties of a generic landscape)**

“I think this should get wrapped into the “landscape in practice section”. Basically, in the intro, I think it is good to have a section about what aspects of a landscape represent and what kinds a landscape can be used to address.”

**Response:** It’s worth saying something about landscape properties earlier (in qualitative terms), like in the intro. But I think a precise mathematical discussion of properties of landscapes is absolutely crucial, and can be one of our major contributions. We are trying to clarify what a landscape means in a precise quantitative sense, so I think it is important to be both quantitative and precise.

Like I said above, I think this section could be one of the lead-ins to our “definitions” of landscapes.

**Comment: (on “Should be agnostic to the underlying kind of model…”)**

“I don’t think this is true. These are fundamentally different ways of thinking about a system.”

Response: I vehemently disagree. If “real biology” is operating at the CME level (or even deeper), shouldn’t our landscape be defined at that level? Besides, various landscape constructions and related ideas (P\_ss, transition paths) are defined at the CME level.

I think this is an important point to make that we should make, since I haven’t seen it made elsewhere.

**Comment: (on Things a landscape can capture)**

“I would move this into the “landscapes in practice” section toward the end of the intro.”

**Response:** Some qualitative discussion should certainly go there. But I also wanted to put some more technical/mathematical discussion here.

As I said above, this section can be one of the lead-ins to our “definitions” of landscapes.

**Comment: (on DIFFERENT LANDSCAPES)**

“We will have to decide which of these to focus most on. We don’t have to be comprehensive here since it is not really that type of review.”

**Response:** Agreed.

**Comment: (on Markov chain landscape)**

“Not familiar with this one. Probably a good one to include though since it gets you into discrete landsapes.”

**Response:** Not sure what to call it (I’ll think more about this), but I’m sure you’ve seen this before. This is where people bin cell states into discrete types and just talk about transition rates between them, or the relative stability of those cell types. Ex: there was a quantitative biology seminar talk in spring (the one with the cancer attractors and the art of the lady holding scales) that used this notion of a landscape.

Also, I think it goes great here since it is conceptually/mathematically the simplest, and satisfies all the reasonable requirements of a landscape.

**Comment: (on Steady state Fokker-Planck landscape)**

“Definitely yes.”

**Response:** Agreed.

**Comment: (on Freidlin-Wentzell/stochastic path integral-derived quasi-potentials)**

“Maybe, will discuss.”

**Response:** I think it’s important because it is the “canonical” example of a landscape that tells you legitimate transition path information. No other landscape really does this. Plus, we will have to discuss transition paths anyway, so we might as well get our feet wet here.

**Comment: (on A-type integral and SDE decomposition)**

“I think this may be too much in the weeds.”

**Response:** Maybe. But we should keep in mind that Ao seems influential in landscape biology, and there are many papers about his construction. Sui Huang cited him in his 2012 RSIF paper, and compared his method to the normal decomposition and talked about how they agreed in certain situations.

**Comment: (on Vector decomposition landscapes)**

“Definitely yes. Also keep in mind that Sui will likely be a reviewer.”

**Response:** Agreed and good to know. (How do you know?)

**Comment: (on General comments on how landscapes have been applied)**

“Belongs earlier in the extended intro. Others are good.”

**Response:** Good point, will change.

**Comment: (on THE LANDSCAPE IN PRACTICE)**

“I think this should be two explicitely different sections.

A section that provides a guide as to what types of problems each landscape may be useful for.

A second section on the pitfalls, challenges, and issues that more research is needed to address.”

**Response:** Good point, will change.