∂a∂i: Diffusion Approximations for Demographic Inference

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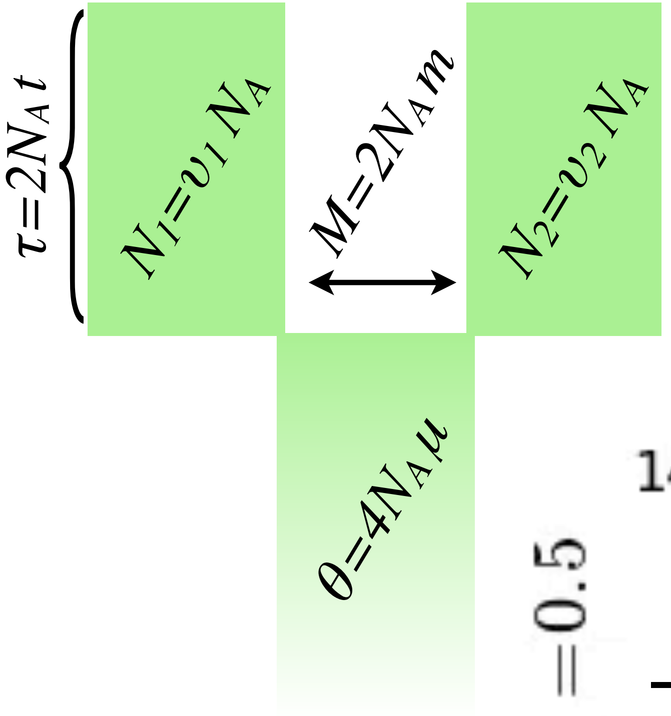
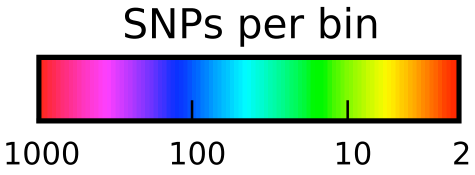
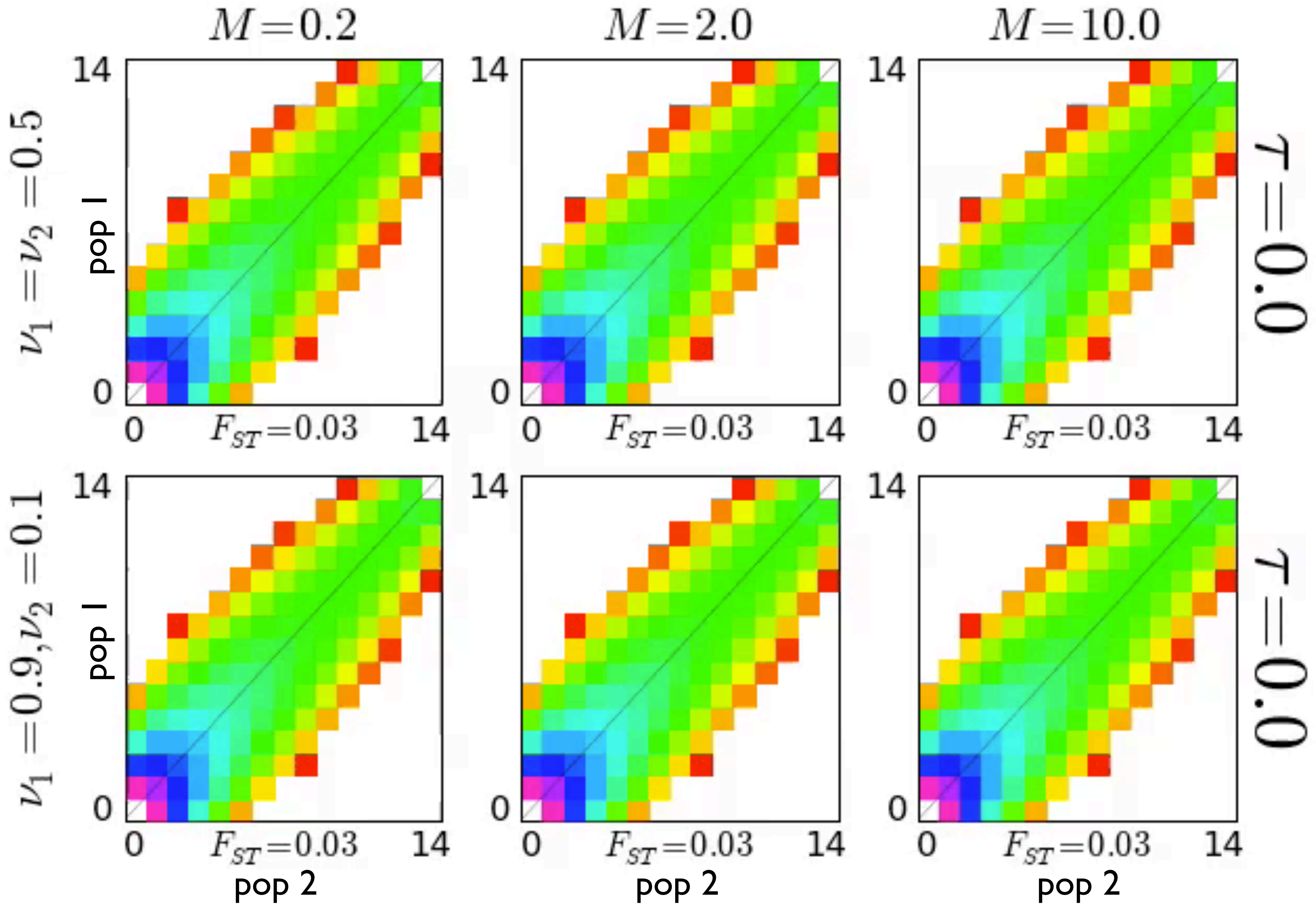
http://bitbucket.org/gutenkunstlab/dadi/
http://groups.google.com/group/dadi-user

Frequency spectrum gallery



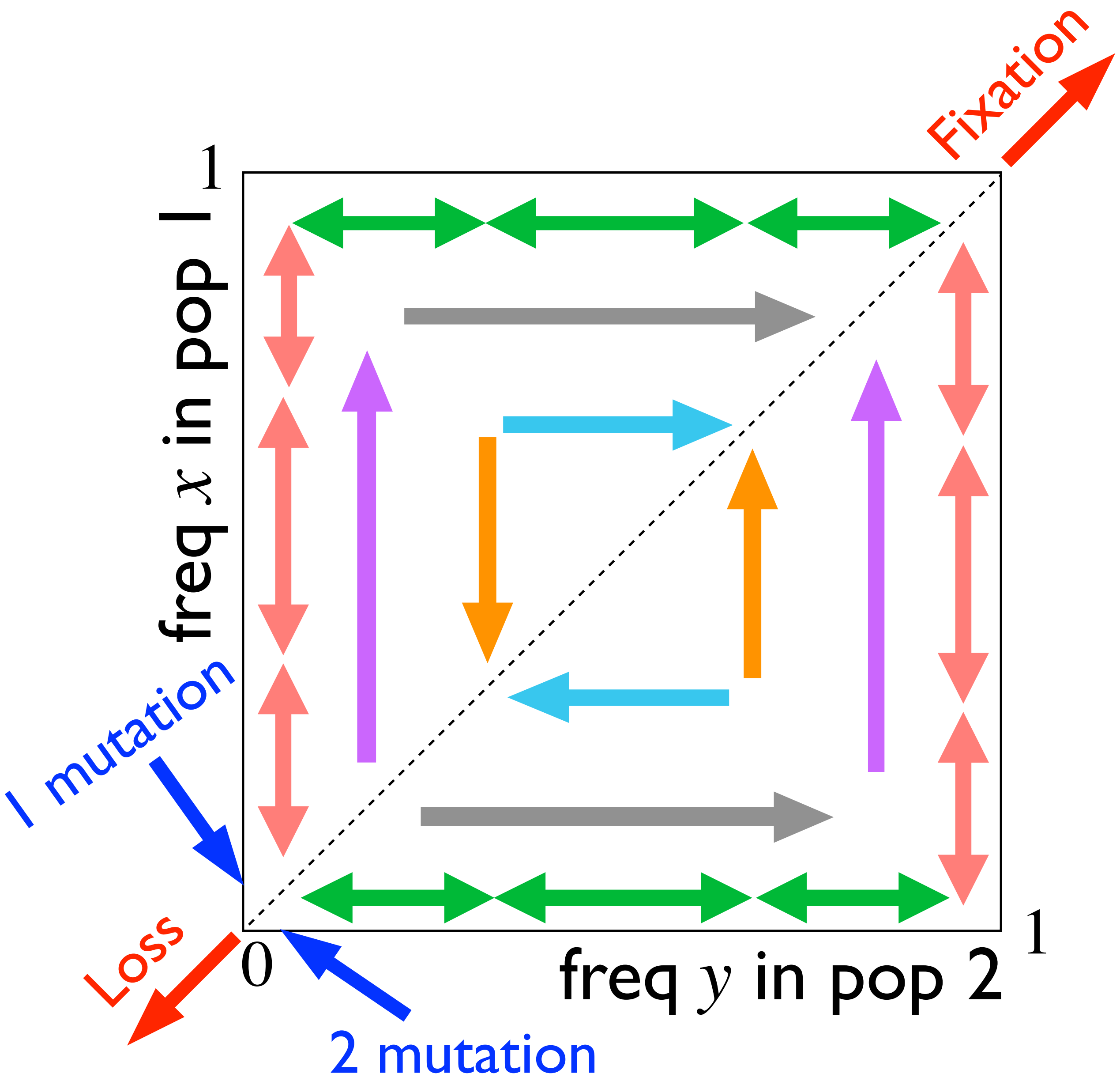




Diffusion simulation of joint AFS

$\phi(x,y,t)$: density of SNPs at freq x in pop 1 and y in pop 2.

$$\frac{\partial\phi}{\partial\tau} = \frac{1}{2}\frac{\partial^2}{\partial^2 x}\left[\frac{x(1-x)}{\nu_1}\phi\right] - \frac{\partial}{\partial x}\left[\left(M_{1\leftarrow 2}(y-x) + \gamma_1 x(1-x)\right)\phi\right]$$
$$+\frac{1}{2}\frac{\partial^2}{\partial^2 y}\left[\frac{y(1-y)}{\nu_2}\phi\right] - \frac{\partial}{\partial y}\left[\left(M_{2\leftarrow 1}(x-y) + \gamma_2 y(1-y)\right)\phi\right]$$



Splittings

Pop 2 diverges from pop 1:

$$\phi(x,y) = \phi(x)\,\delta(y-x)$$

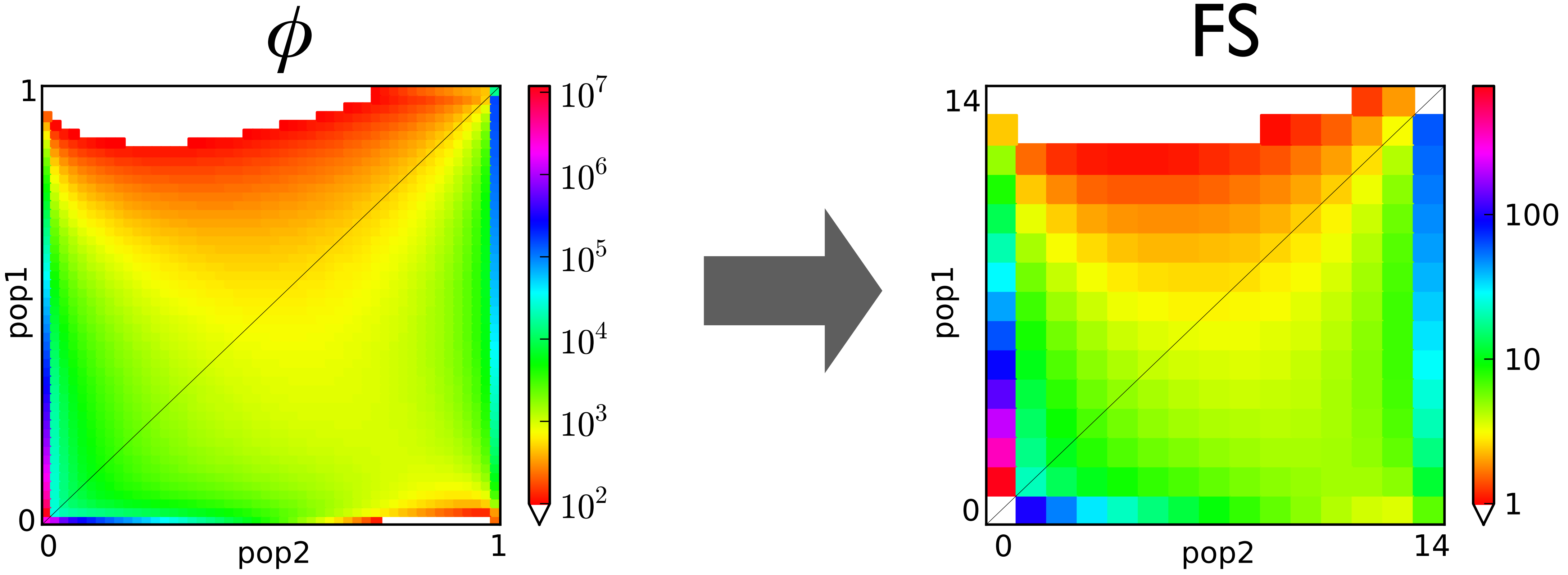
Numerical solution via alternating direction implicit finite-difference method

Gutenkunst et al.
PLoS Genet (2009)

ϕ to spectrum to likelihood

$$FS[i,j] = \int_0^1 dx \int_0^1 dy \binom{n_1}{i} x^i (1-x)^{n_1-i} \binom{n_2}{j} y^j (1-y)^{n_2-j} \phi(x,y)$$

... can also model (some) ascertainment



$$\text{log-likelihood} = \log\left[\prod_i^{n_1}\prod_j^{n_2} \text{Poisson}\big(\text{drawing Data}[i,j] \big| FS[i,j]\big)\right]$$

... assuming no linkage

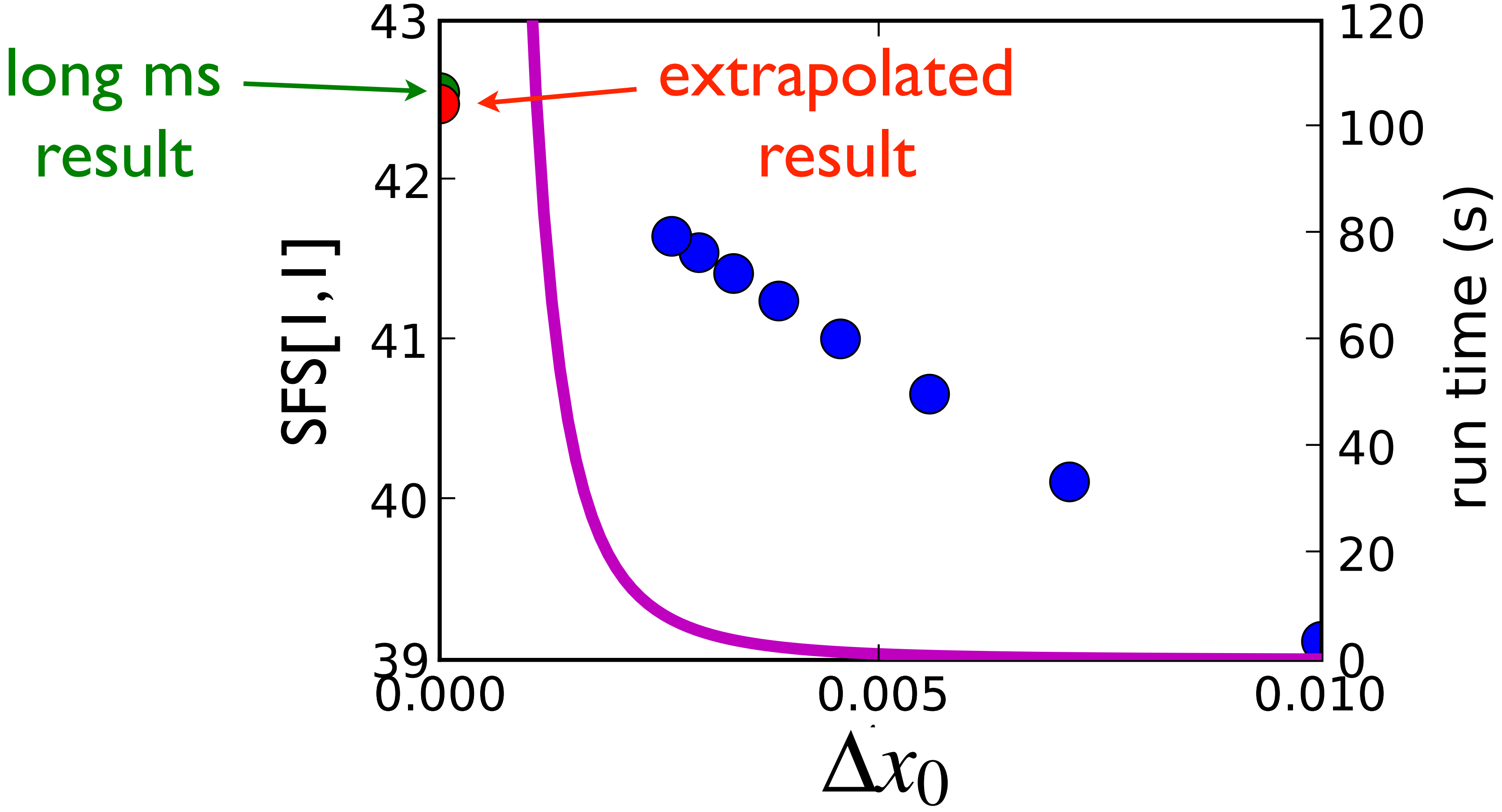
Overcoming finite gridsize

Run time scales as (# grid points)^P.

(e.g. 100x100x100 grid = 10^6 points.)

Solution: Richardson extrapolation

$$\log \mathrm{Calc}[\mathrm{i,j}] = \log \mathrm{Actual}[\mathrm{i,j}] + a\Delta x_0 + b\Delta x_0^2$$



Specifying grid size

- Usually called `pts_l` in scripts.
- Generally want quadratic extrapolation, so `pts_l` should be a list of 3 elements.
- The smallest value should be larger than the largest dimension of your AFS.
- For example, if you have sample sizes of [14, 20, 50] individuals, your AFS will have size [29,41,101]. A good setting for `pts_l` might be [120,130,140].
- If you model involves small population sizes, high migration rates, or strong selection, you get warnings that extrapolation has failed. In that case, you should try increasing `pts_l`.

Parameter optimization

Parameter optimization

- Parameter optimization is an art, not a science. No algorithm can be guaranteed to converge to the true maximum likelihood in general.

- Hence I always recommend multiple optimization runs from different starting points. (The `perturb_params` method helps with this.) You can be confident if you see the same maximum likelihood repeated several times.

- For example, we often run until the best 3 likelihoods found are all within 1% or 0.1% of each other.

- ∂a∂i includes a few optimization algorithms.

Optimization algorithms

- `optimize_log`: Based on BFGS algorithm, which uses derivative information. Fast if your starting point is close to the maximum likelihood.
- `optimize_log_fmin`: Based on Nelder-Mead simplex algorithm, which doesn't use derivatives. Slower, but more robust.
- `optimize_grid`: Basic grid search. Very robust, but very inefficient.

Optimization bounds

- Certain parameter settings cause AFS evaluation to be extremely slow, so you should set bounds to avoid those ranges.
- Avoid small population sizes, so maybe set lower bound ~ 1e-3.
- Avoid long divergence times, so maybe set upper bound ~ 5.
- Avoid high migration rates, so maybe set upper bound ~ 10.

Implicit θ

- The overall genetic diversity of the populations is set by $\theta = 4N_a\mu L$. Here N_a is the ancestral population size, µ is the per-base mutation rate, and L is the length of sequence.

- It turns out that the optimal θ for any demographic model is easy to compute once the other parameters are set, so by default it isn't explicitly included in ∂a∂i models. In this case, you use the `_multinomial` methods.

- In some cases, you may want to hold the parameter θ fixed, which you can do.

Ancestral states

- Your inference will have the greatest power if you have ancestral states, to call derived versus ancestral alleles.
- But even with a good out group (e.g. human vs. chimp), you'll still have some misidentification.
- This can be corrected statistically (Hernandez et al. (2007)), but it's a little touchy.
- You can just fold the spectrum, and only consider minor vs major alleles.
- But now we typically just misidentification as a model parameter.

Missing data

- If your data are incompletely called, not all SNPs may be called for all individuals.
- If only a small portion of SNPs are missing, they can be dropped from the analysis (and *L* adjusted).
- But if this is a common problem, our current solution is to *project* the SNPs downward to a common sample size. You then discard SNPs with fewer calls than this smaller sample size.
- The projection is essentially averaging over all resamplings of a smaller number of samples from your called samples.

Parameter uncertainties

- The most robust way to estimate parameter uncertainties is via bootstrap.
  - Divide your data into large ~unlinked blocks.
  - Generate many resampled data sets from those blocks.
  - Fit those resampled sets to estimate confidence intervals.
- Bootstrapping this way is very computationally expensive.
- Recently, we've used an approximation based on Godambe information, which is much faster to compute.

Suggested workflow

- Don't jump in by fitting the most complicated model you can conceive!
- Start by fitting very simple models to single populations.
  - This will both give you quick experience running ∂a∂i and insight into what demographic events happened in the past to your population.
  - For example, if your 1D fits indicate population growth, make sure that's included in your 2D fits.
- Use residual plots and comparison of likelihoods to judge which parameters to add for next model.
- This can be formalized in likelihood ratio tests.

Exercise time!