Modeling Intra-Host Adaptation of Hepatitis C Virus

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Joint work with

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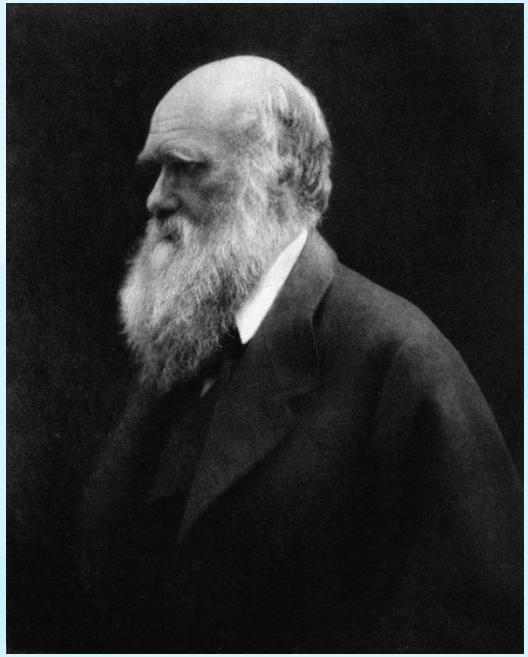
“I deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics, for men thus endowed seem to have an extra sense”

Charles Darwin



Hepatitis C virus

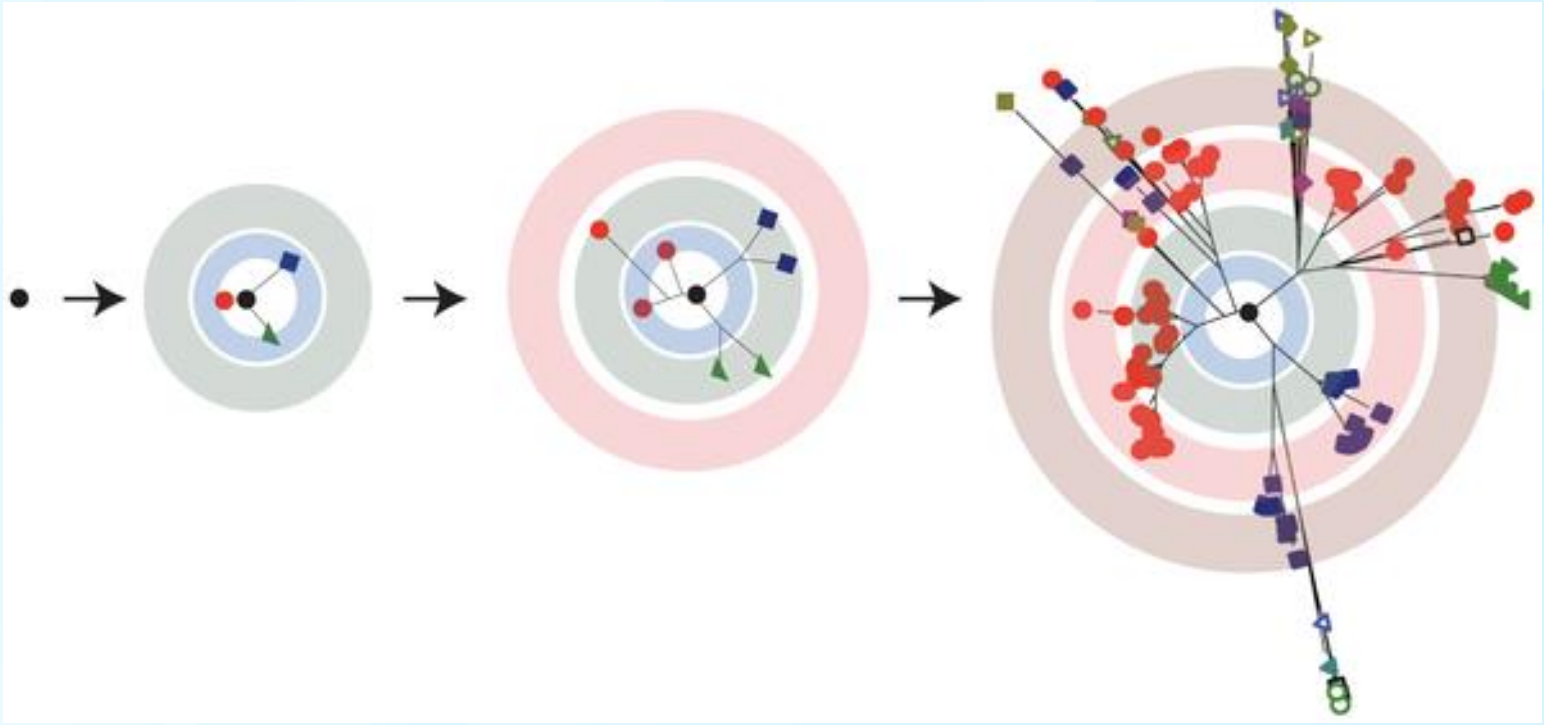
HCV is an RNA virus

HCV infects 2.2% of the world's population

HCV causes chronic liver infection in up to 80% of infected individuals. It is a leading cause of liver cancer. HCV causes more deaths in USA than HIV

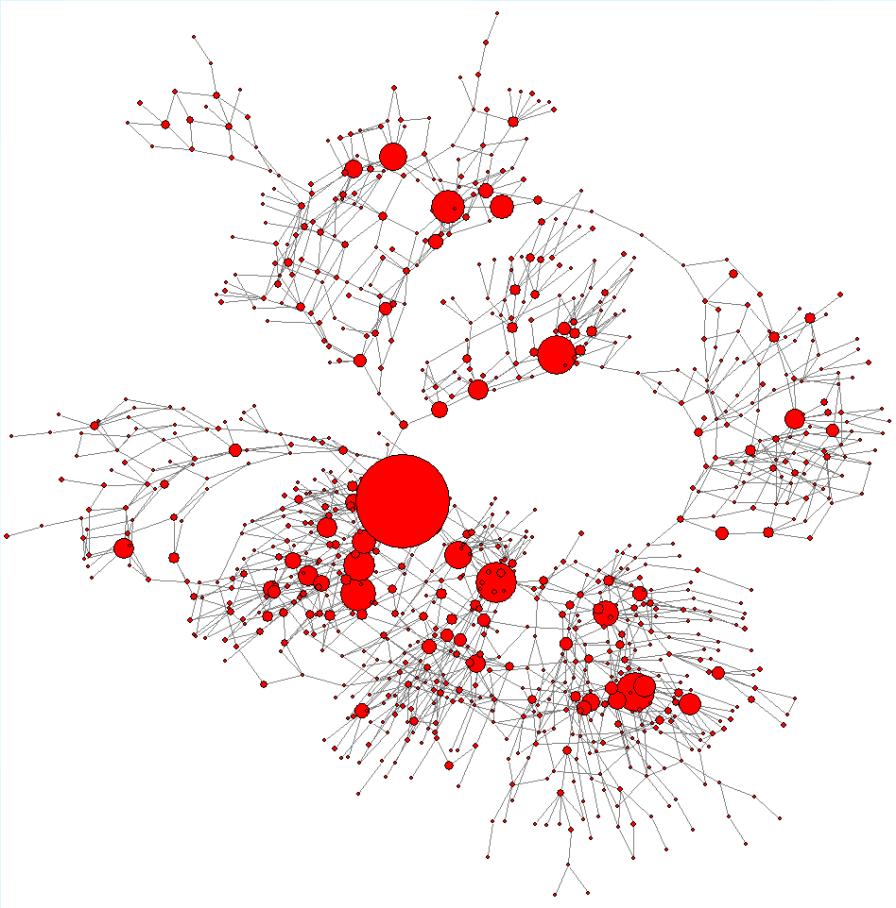
RNA viruses

High mutation rate (~10^{-4} -10^{-5})



Lauring & Andino, PLoS Pathogens 2011

HCV exists in infected host as a large heterogeneous population of intra-host variants (*quasispecies*) evolving in the *sequence space*



Median Joining Network of HCV quasispecies for a chronically infected patient

D. Campo et al., BMC Genomics (2014), 15 (Suppl. 5), S4

Quasispecies Theory

$$\dot{v}_i(t) = \sum_{j=1}^{n} f_j q_{j,i} v_j(t) - \phi(t) v_i(t), \quad i = 1, \ldots, n$$

$v_1(t),\ldots,v_n(t)$ – frequencies of n variants at time t

$f_1,\ldots,f_n$ – replication rates (fitnesses) of n variants, $f_i > 0$

$q_{i,j}$ – probability, that replication of genome i produces genome j

$$\phi(t) = \sum_{i=1}^{n} f_i v_i(t)$$

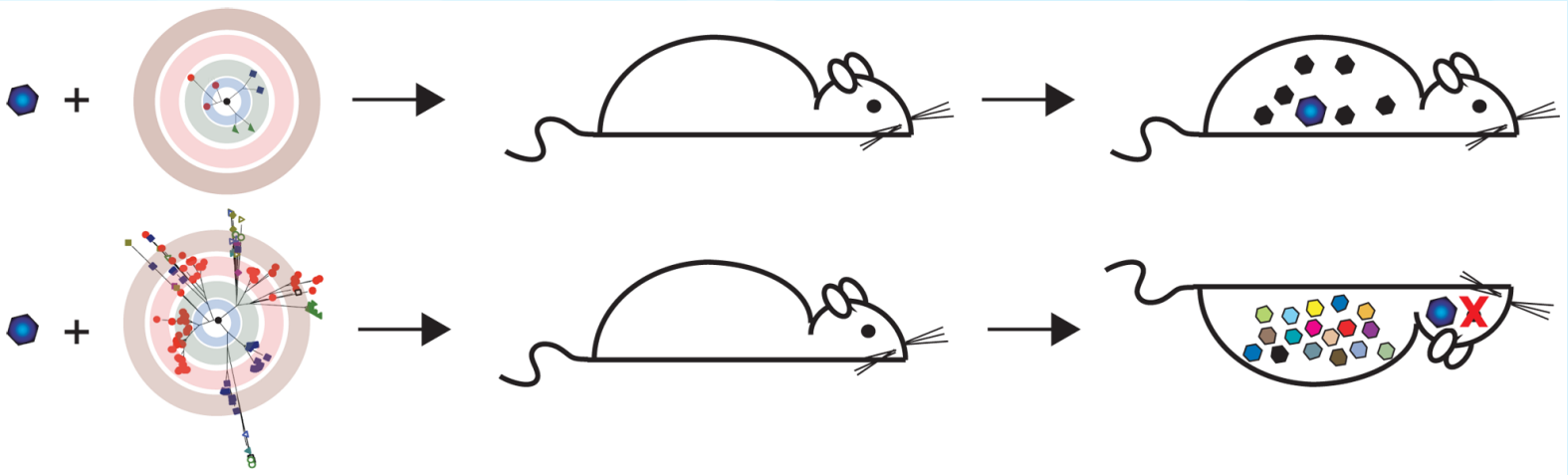
- avarage fitness of the population

Main prediction: survival of the flattest
(in contrast to survival of the fittest)

Viral Population = Quasispecies

Variants differ in

- Virulence
- Escape immune response
- Resistance to antiviral therapies



Lauring & Andino, PLoS Pathogens 2011

Modelling viral evolution

PNAS

Antigenic cooperation among intrahost HCV variants organized into a complex network of cross-immunoreactivity

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Hepatitis C virus (HCV) has the propensity to cause chronic infection. Continuous immune escape has been proposed as a mechanism of intrahost viral evolution contributing to HCV persistence. Although the pronounced genetic diversity of intrahost HCV populations supports this hypothesis, recent observations of long-term persistence of individual HCV variants, negative selection increase, and complex dynamics of viral subpopulations during infection as well as broad cross-immunoreactivity (CR) among variants are inconsistent with the immune-escape hypothesis. Here, we present a mathematical model of intrahost viral population dynamics under the condition of a complex CR network (CRN) of viral variants and examine the contribution of CR to establishing persistent HCV infection. The model suggests a mechanism of viral adaptation by antigenic cooperation (AC), with immune responses against one variant protecting other variants. AC reduces the capacity of the

and homogeneous under the strong negative selection for years, indicating a high level of intrahost adaptation (9). Certain intrahost HCV variants were observed to persist in infected hosts for up to 16 y (9, 14, 15). These observations suggest that intrahost HCV subpopulations can remain unaffected by the immune system for years over the course of infection.

Second, complex dynamics of HCV populations were observed in infected hosts. The density of intrahost subpopulations was found to fluctuate significantly in the course of chronic HCV infection, with some subpopulations persisting at low frequency for years until becoming dominant or reemerging at later stages of infection after being undetectable for a long time (9, 10, 15, 16).

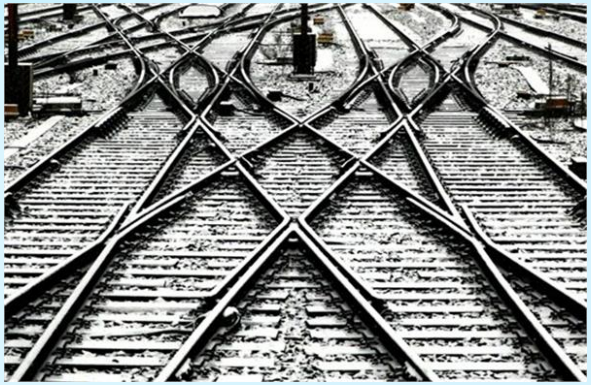
Third, the HCV hypervariable region 1 (HVR1) contains neutralizing antigenic epitopes (17, 18). Significant genetic variation of HVR1 during chronic infection was hypothesized to facilitate escape from neutralizing antibodies (17, 18). However, recent

Goal: to understand how HCV establishes a chronic infection

HCV and immune system

Conventional wisdom: constant immune escape or "arms race" between virus and immune system

Recent observations based on NGS data: everything is more complicated



Facts that do not agree with constant immune escape

- High level of intra-host adaptation
  - negative selection on chronic stages of infection
  - long-living viral variants

- Complex dynamics of subpopulations
  - frequencies fluctuations
  - disappearance and reappearance

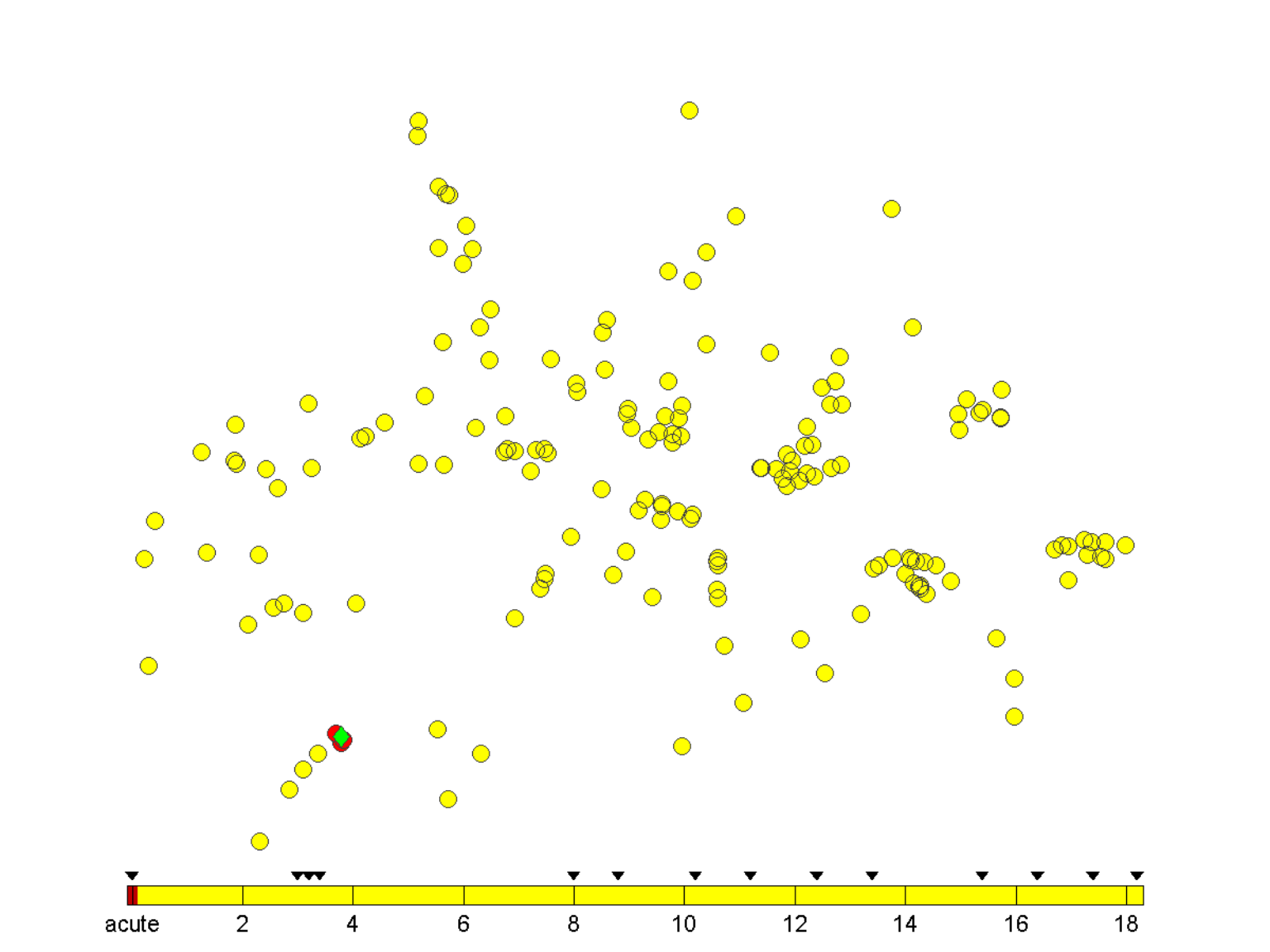
- Antigenic convergence

Ramachandran S et al, Journal of Virology, July 2011, 6369-6380

Viral samples from patients with chronic HCV infection taken at different time points during 9 - 18 years of infection.

2 possible scenarios:

-HCV population continuously diversified, suggesting continuous immune escape.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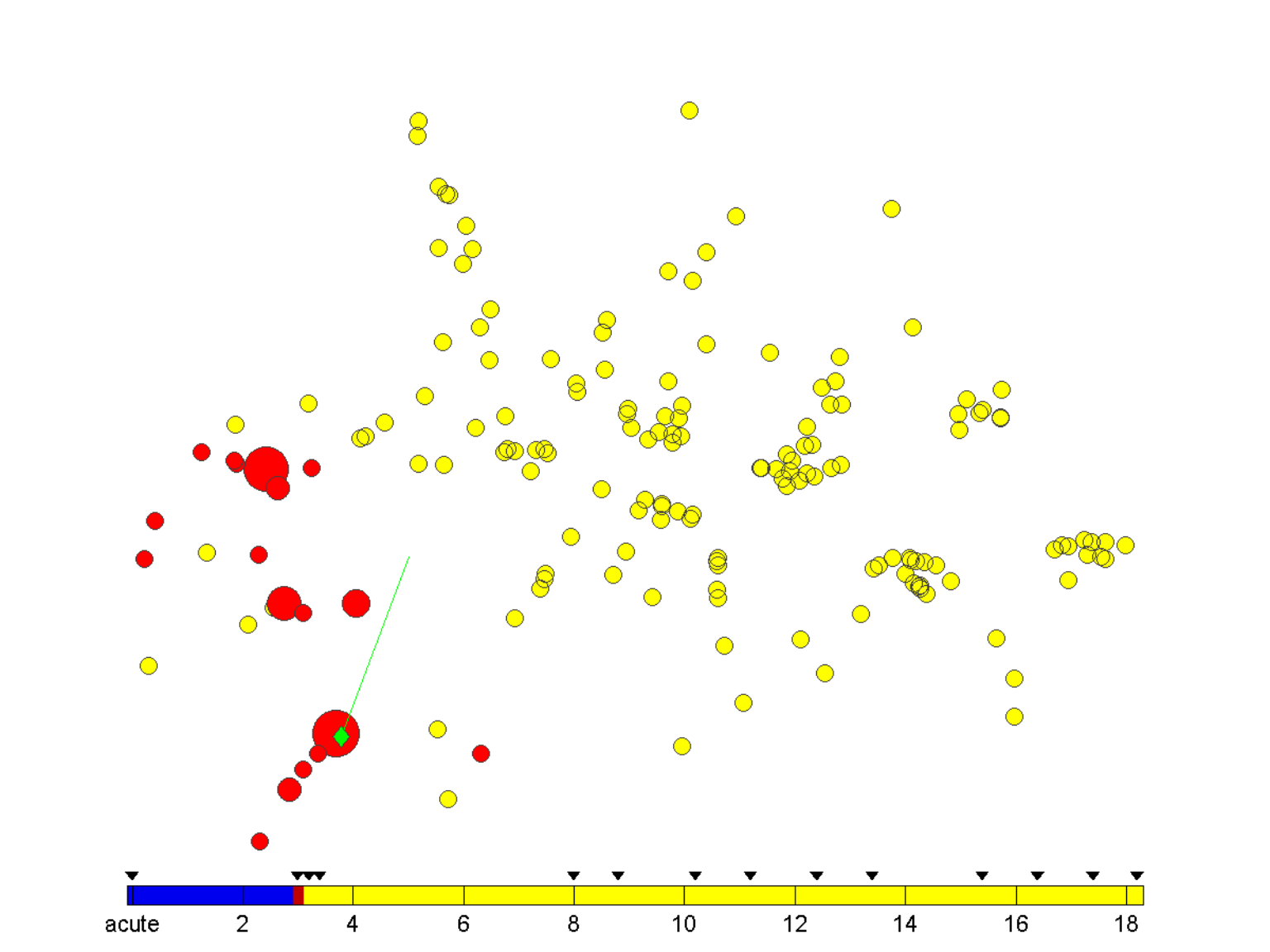
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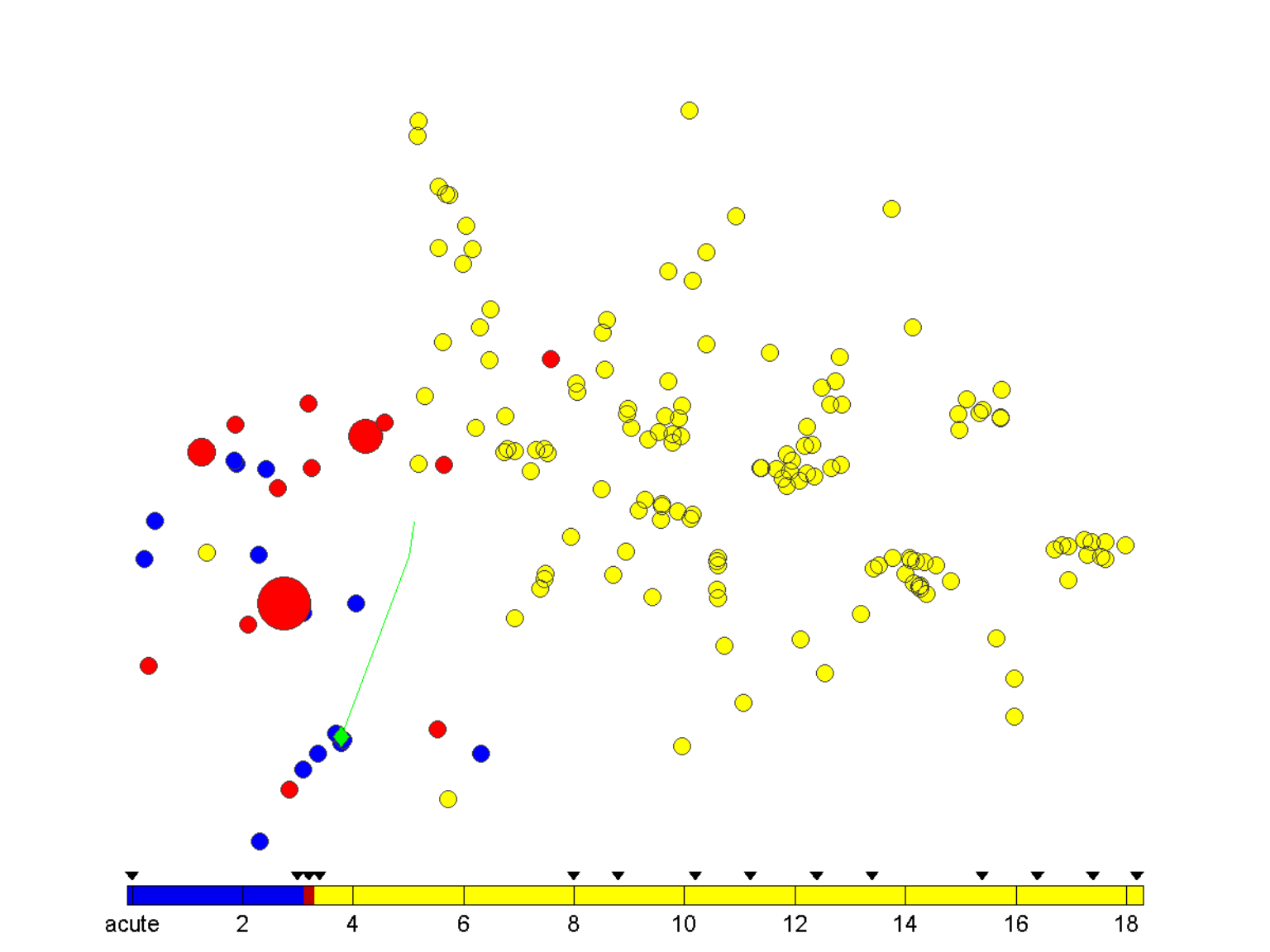
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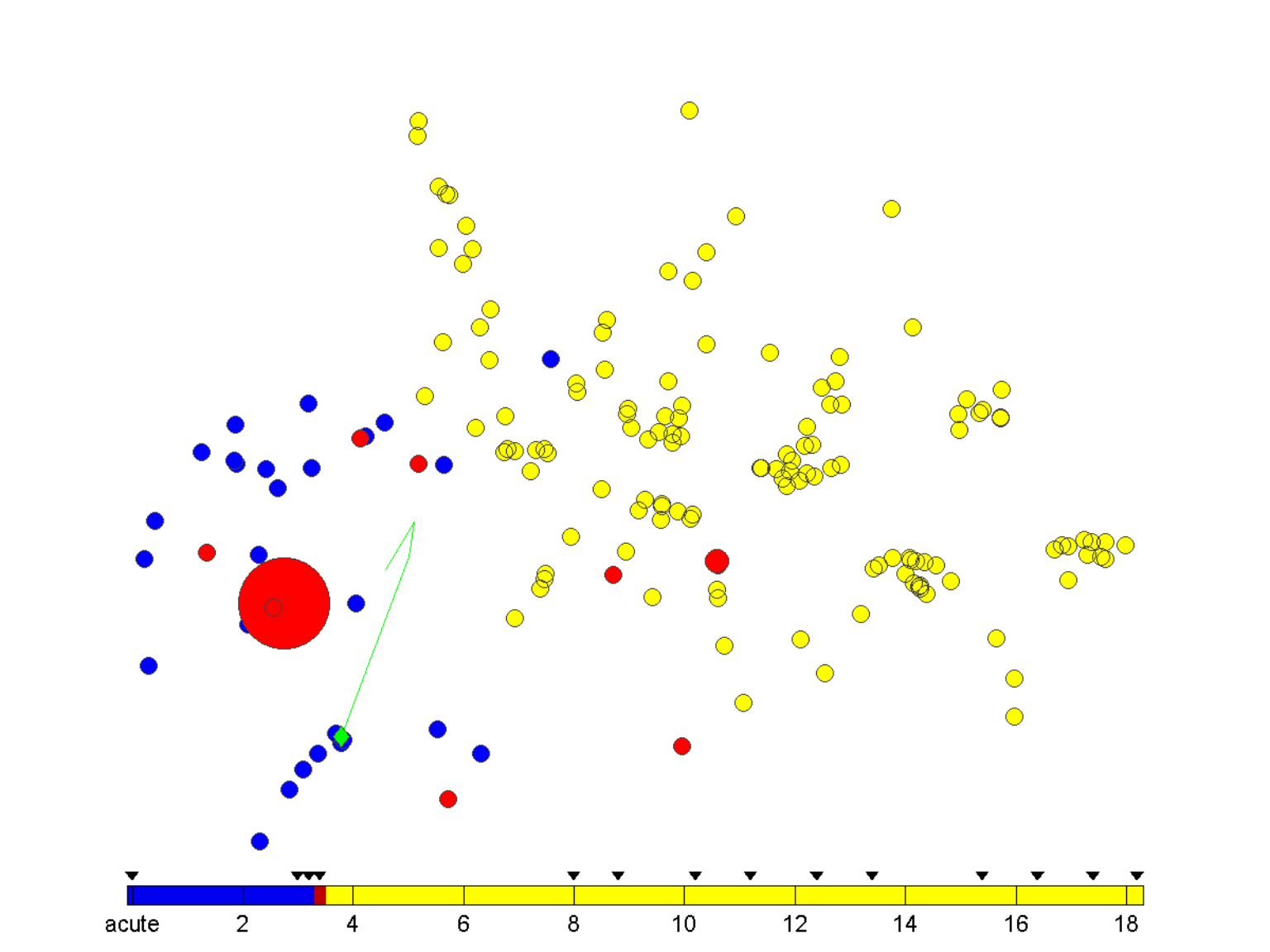
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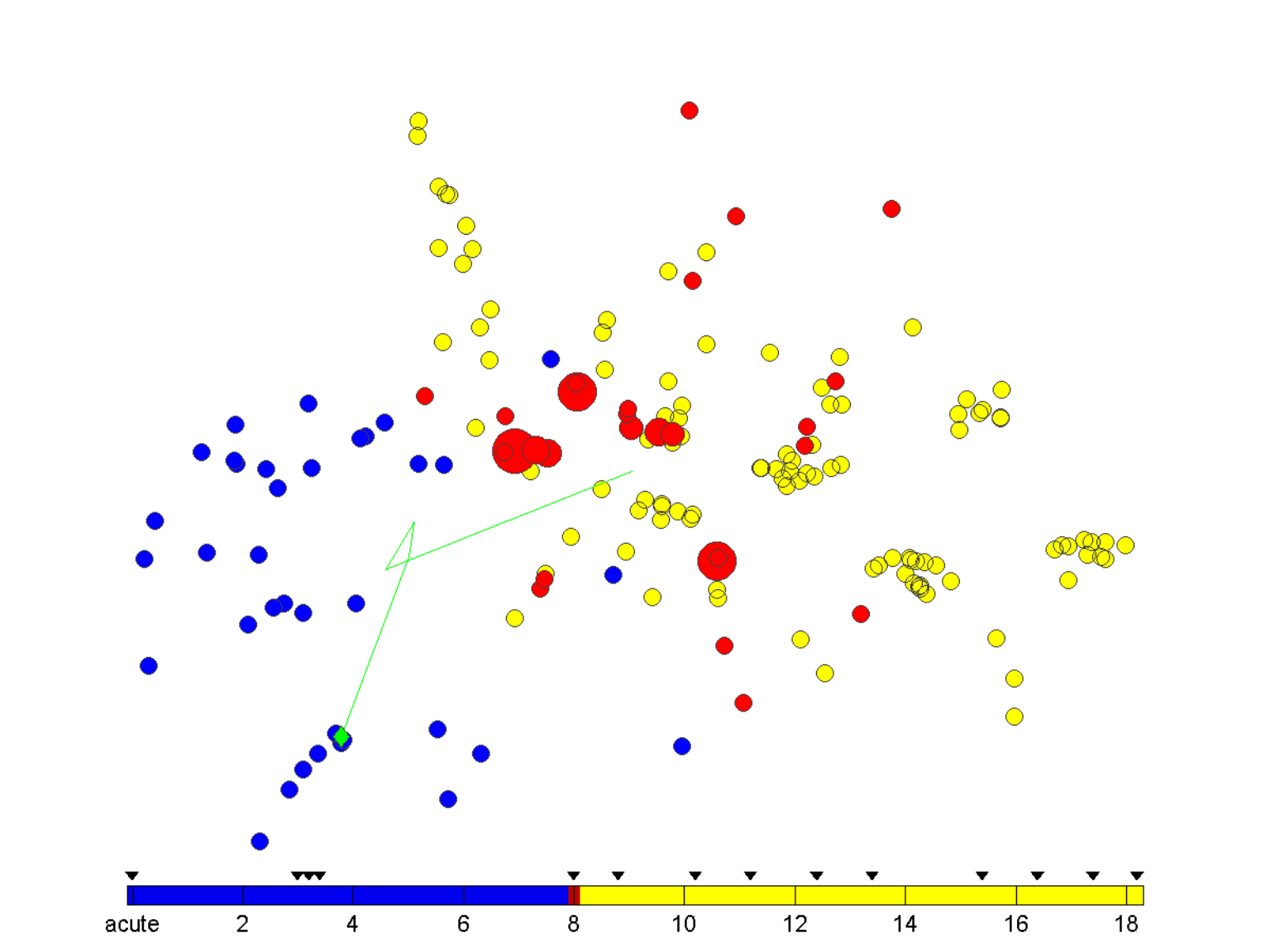
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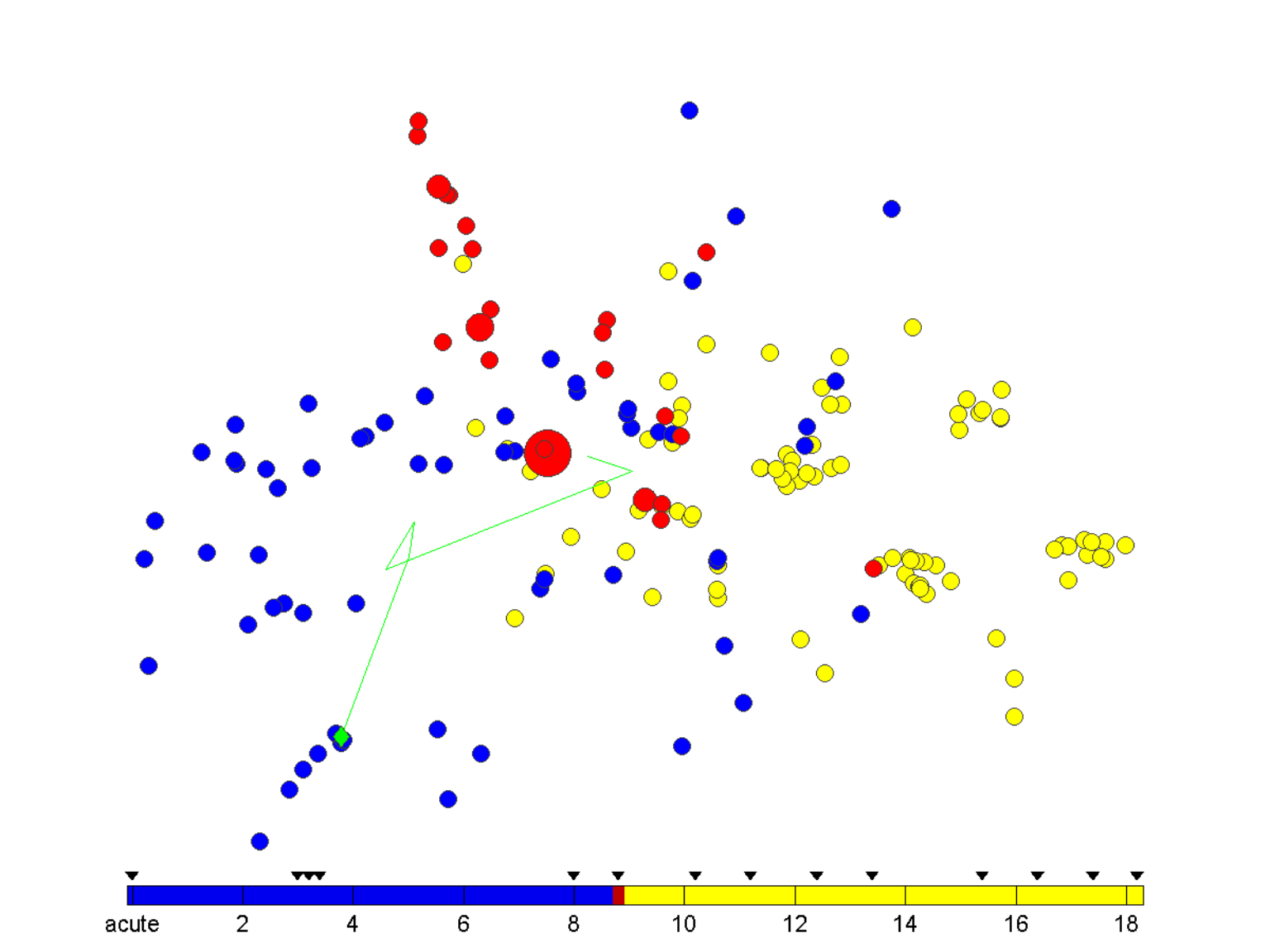
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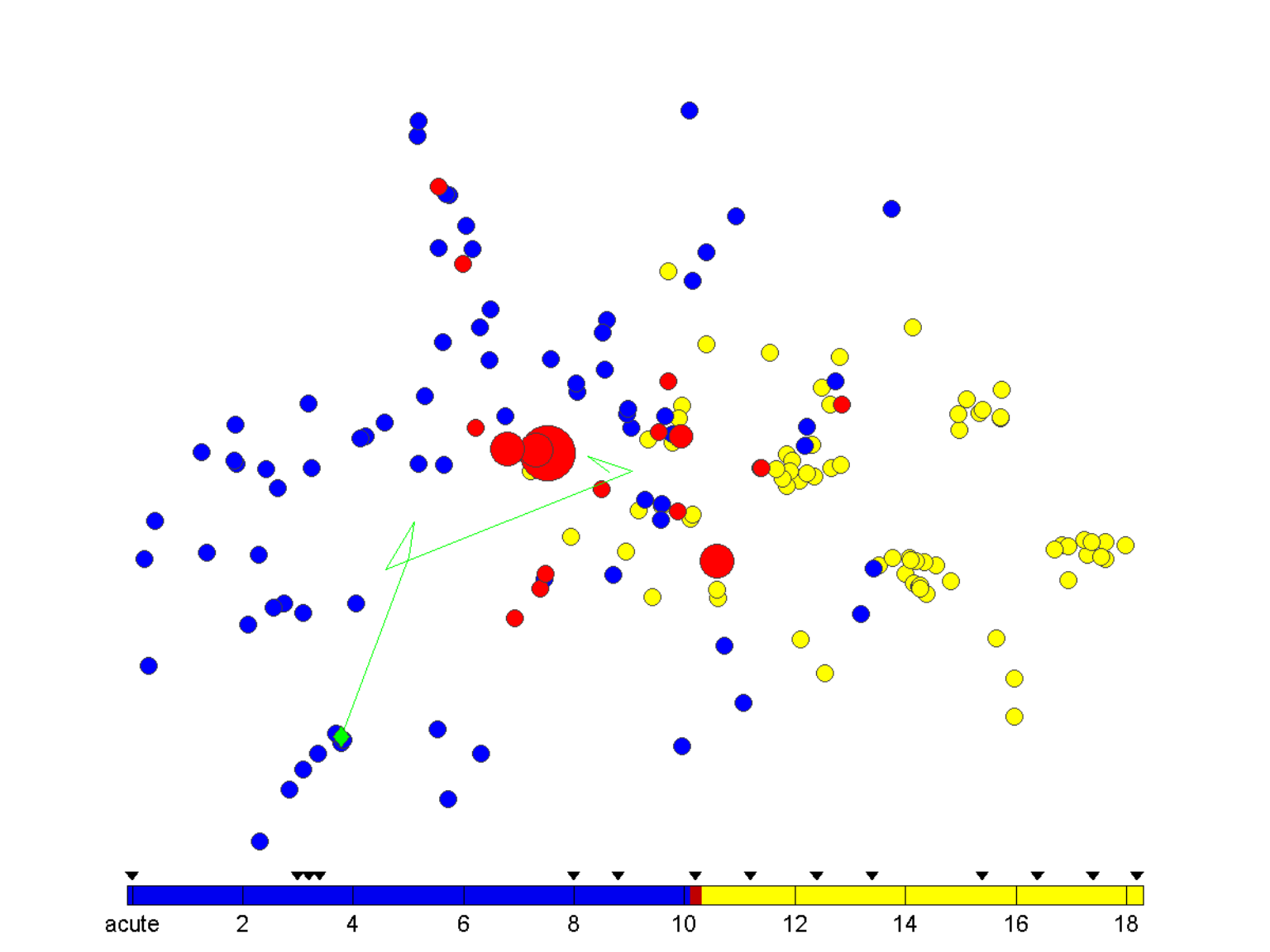
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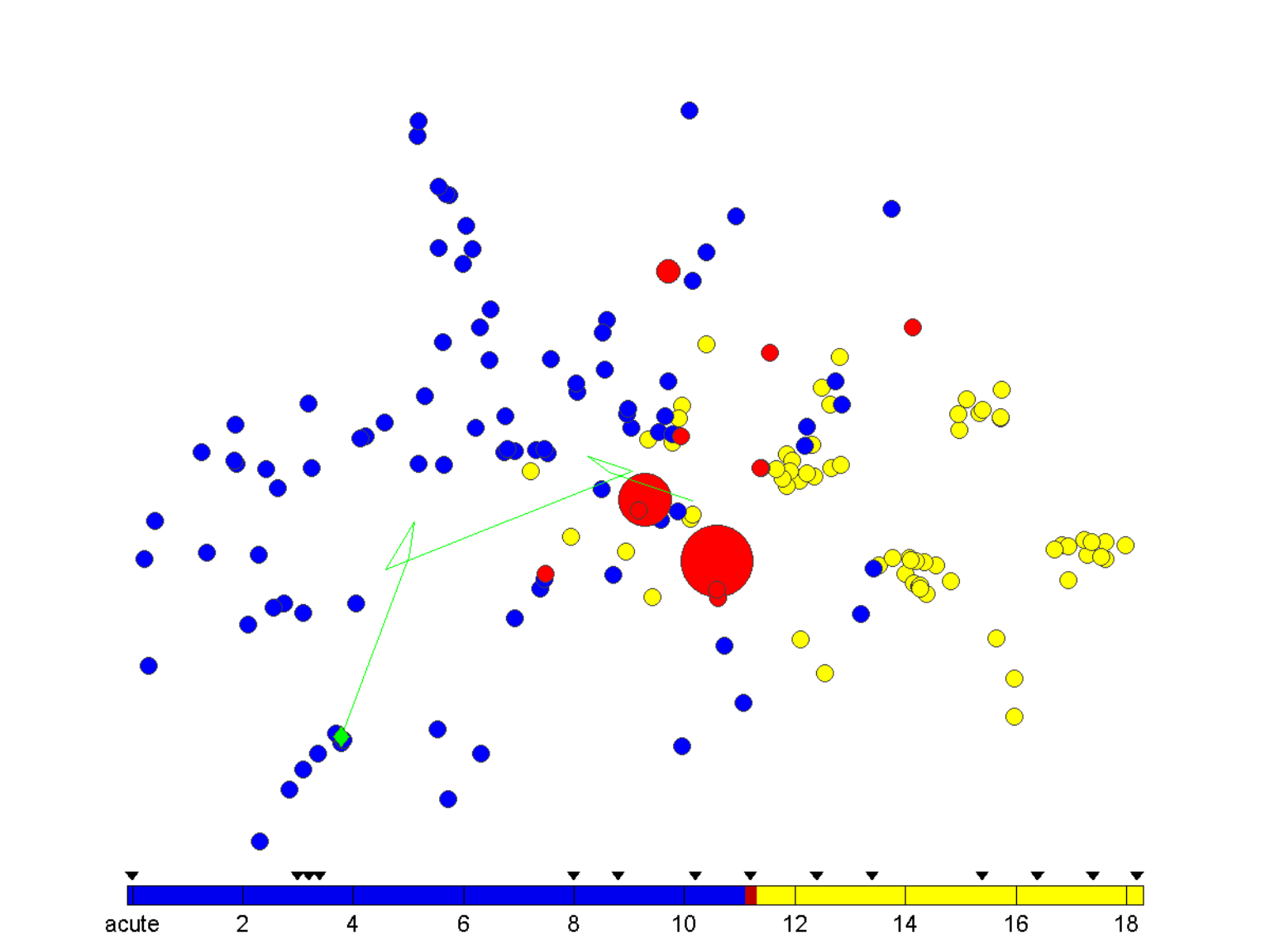
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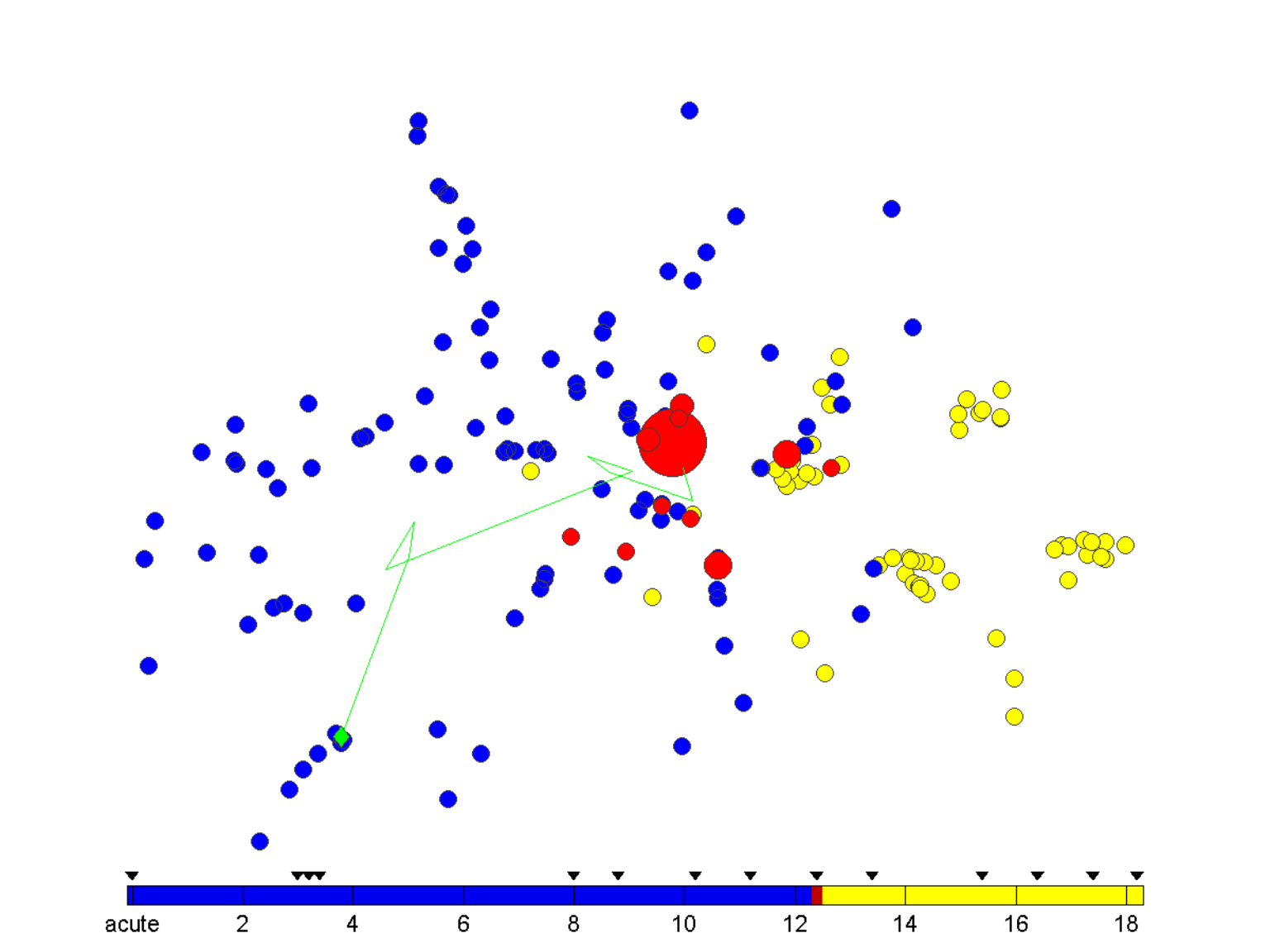
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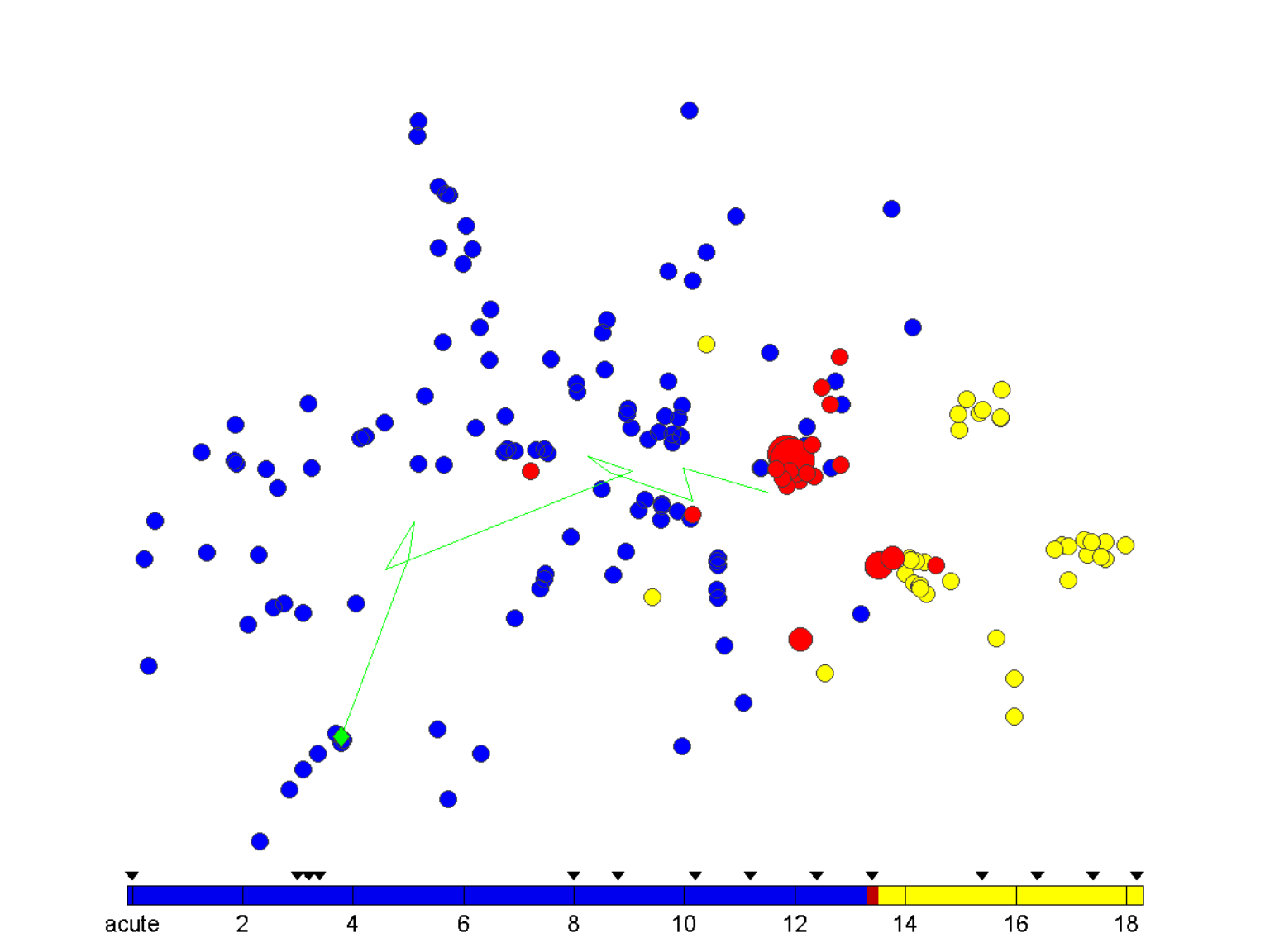
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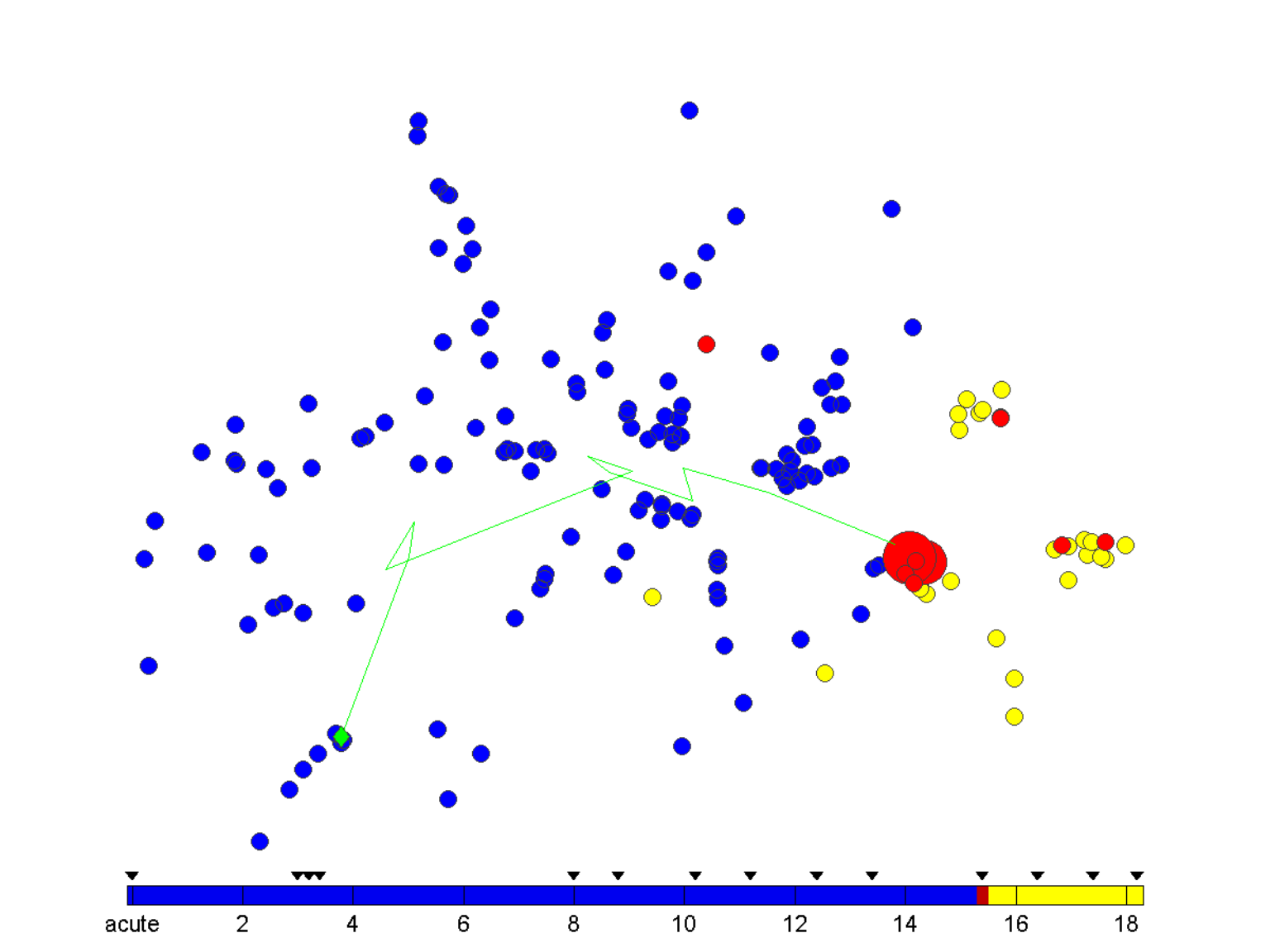
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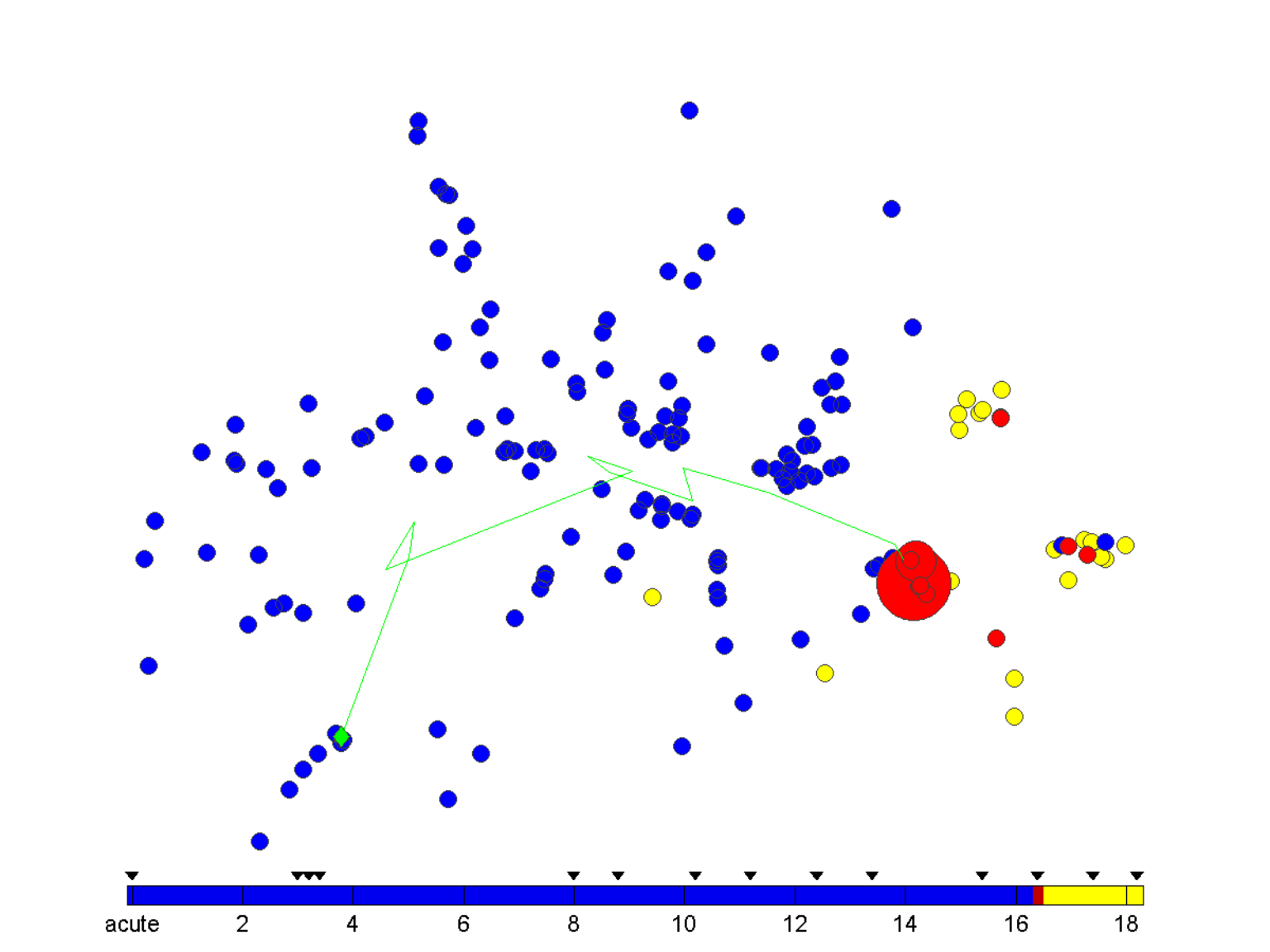
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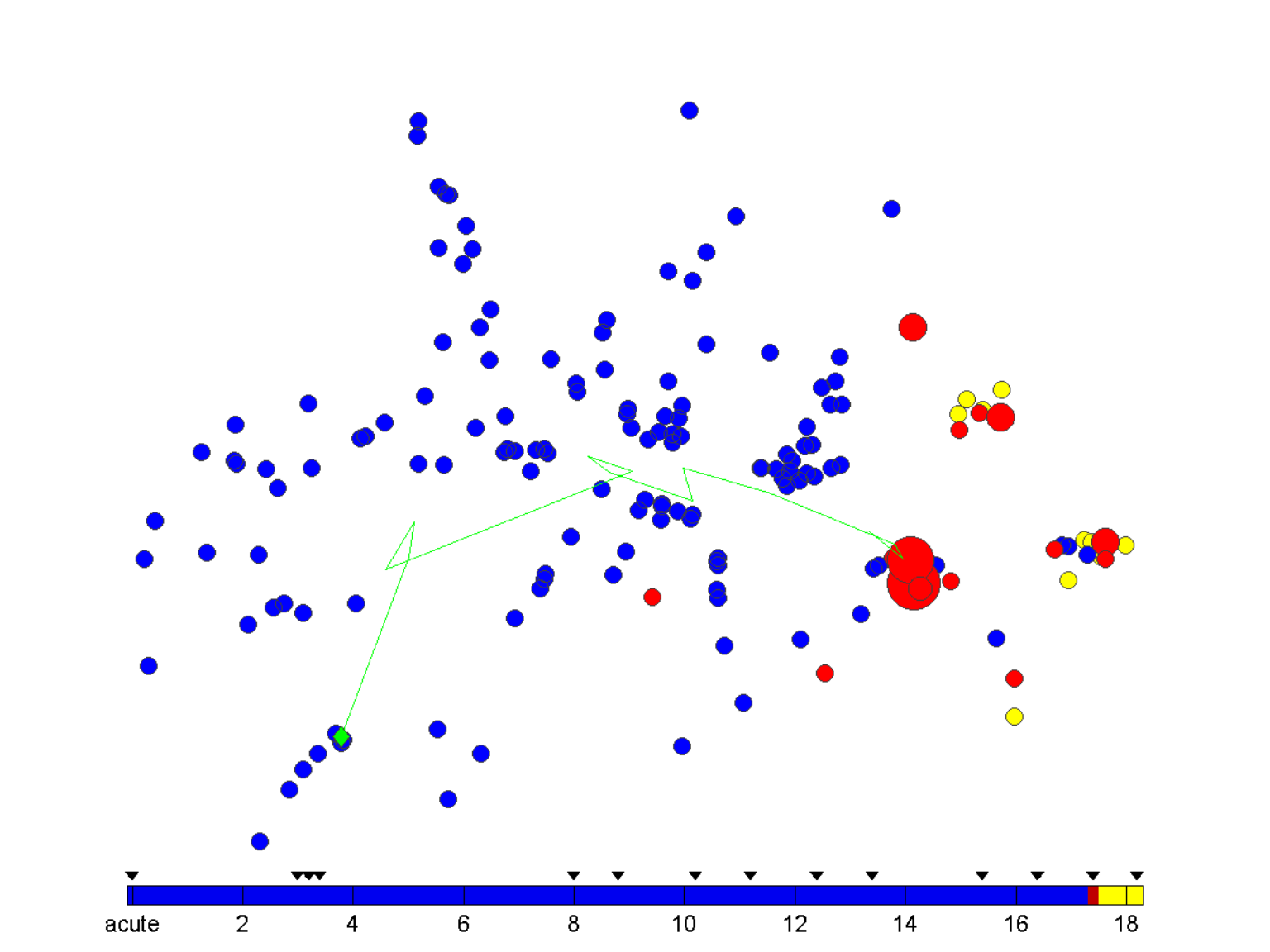
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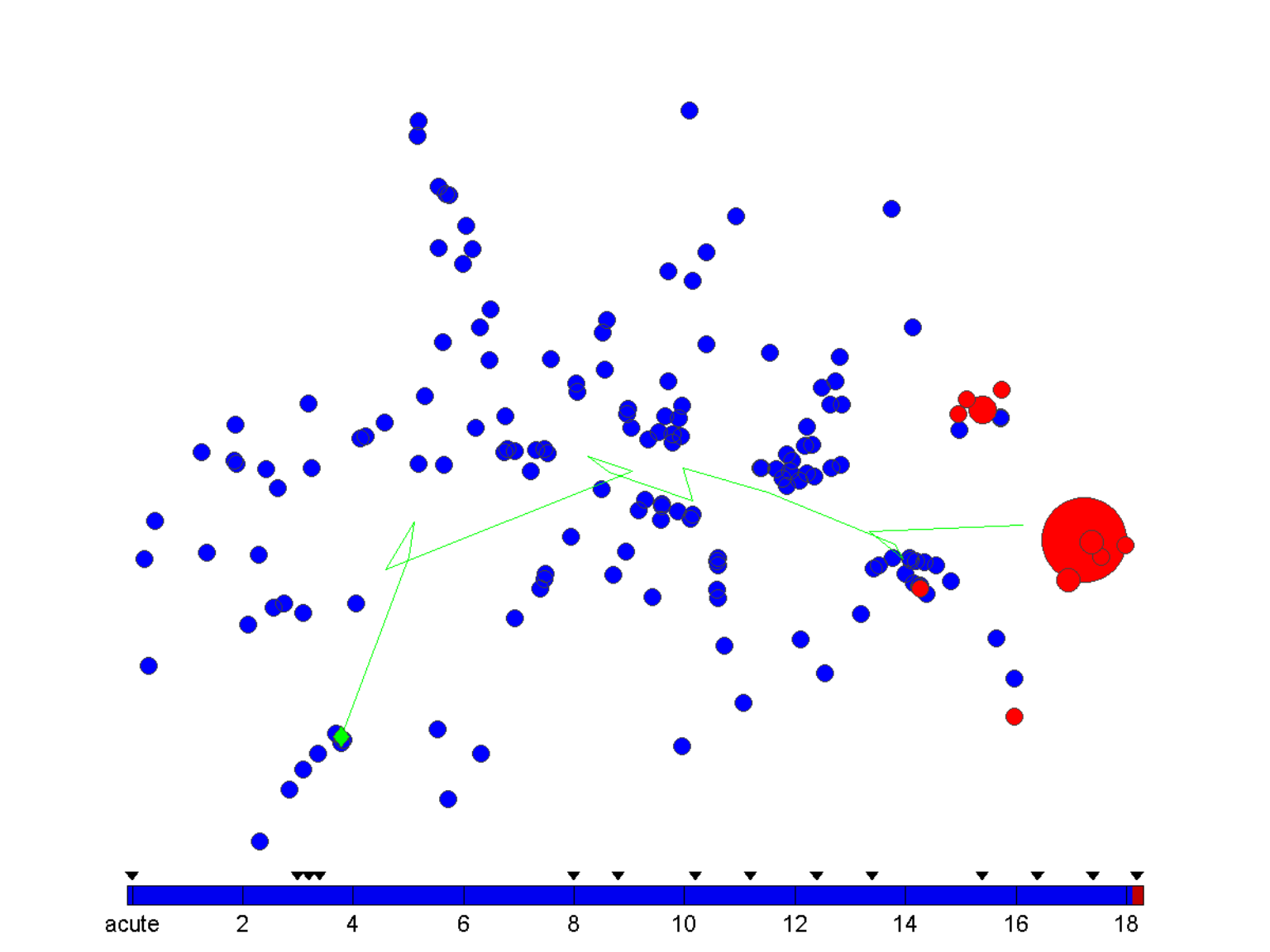
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2 possible scenarios:

-HCV population continuously diversified, suggesting continuous immune escape.

- The viral populations converged into populations evolving within a single community after 9-12 years of diversification. HCV populations were under negative selection at the later stages of infection. One variant was sampled during almost entire observation period (16 years) These observations suggest a high level of intra-host adaptation at late stages of infection.

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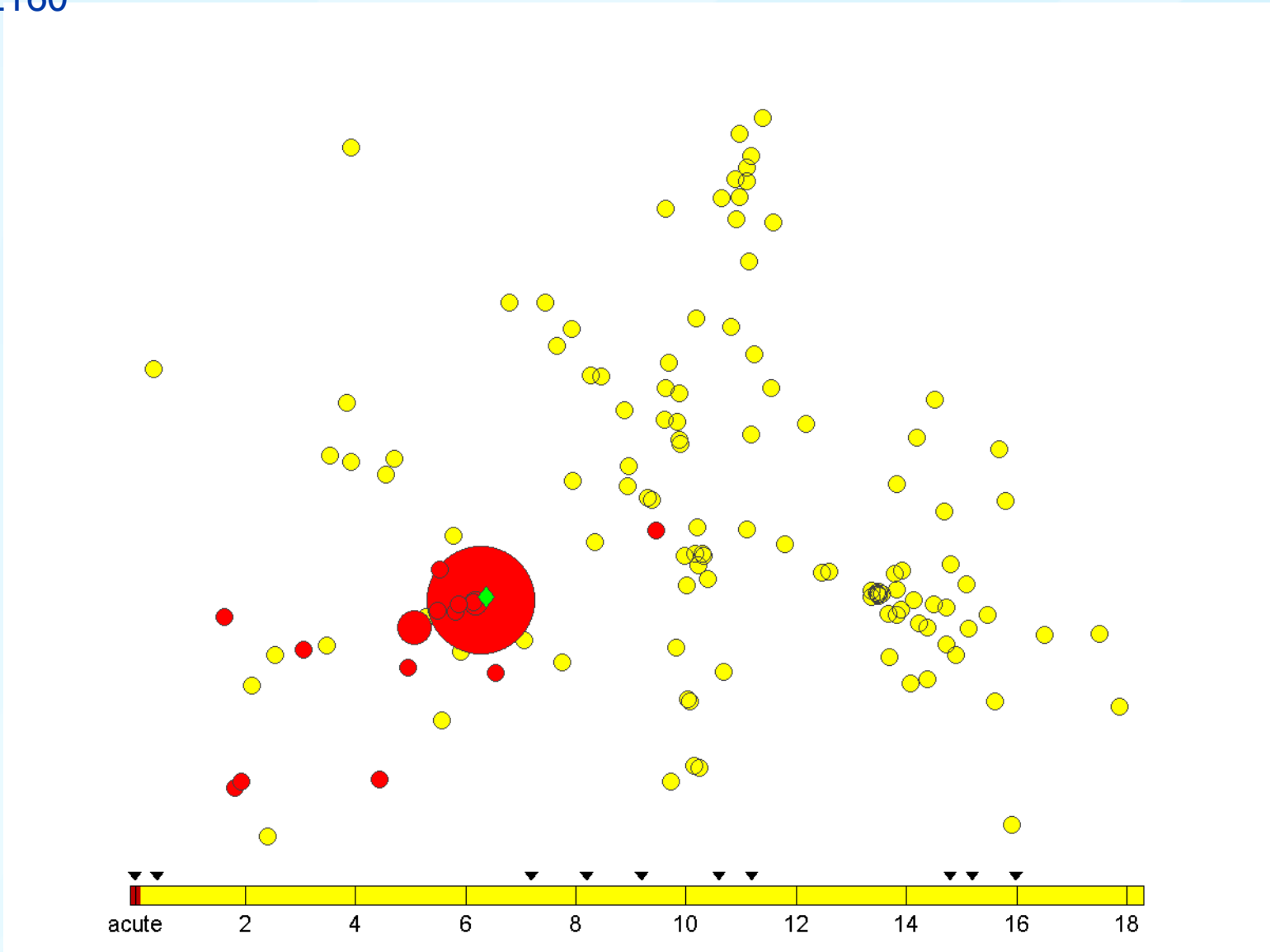

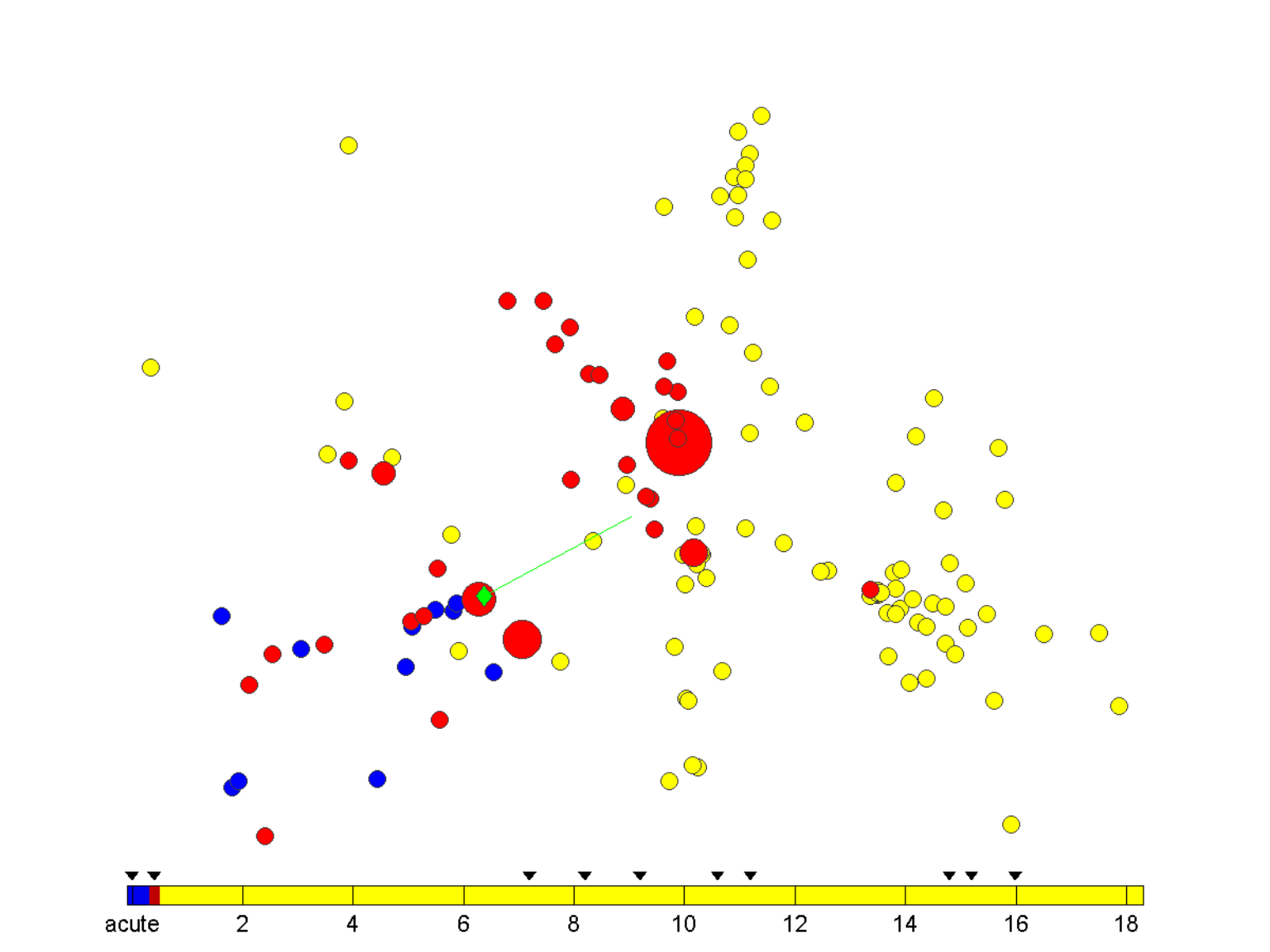
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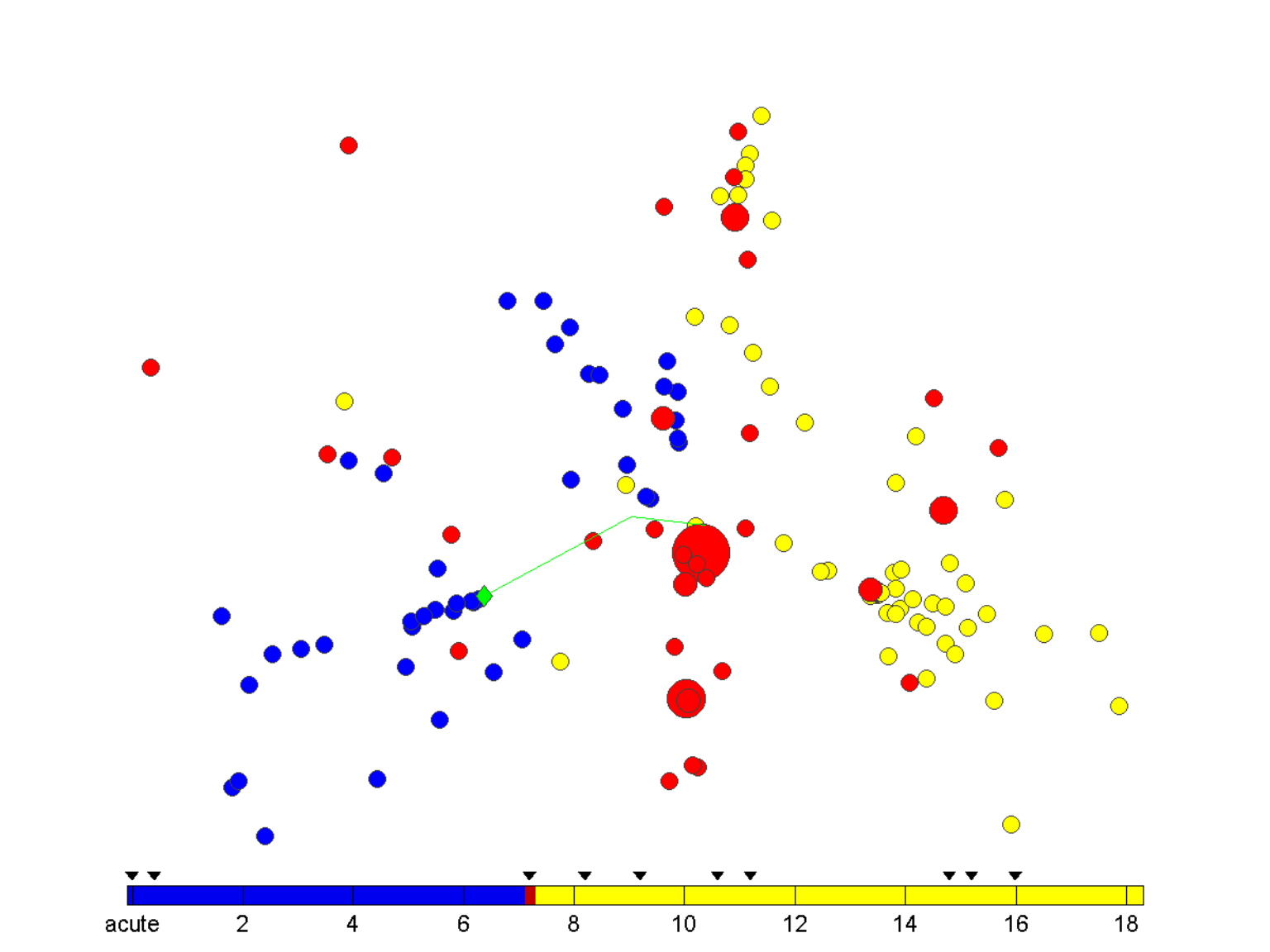
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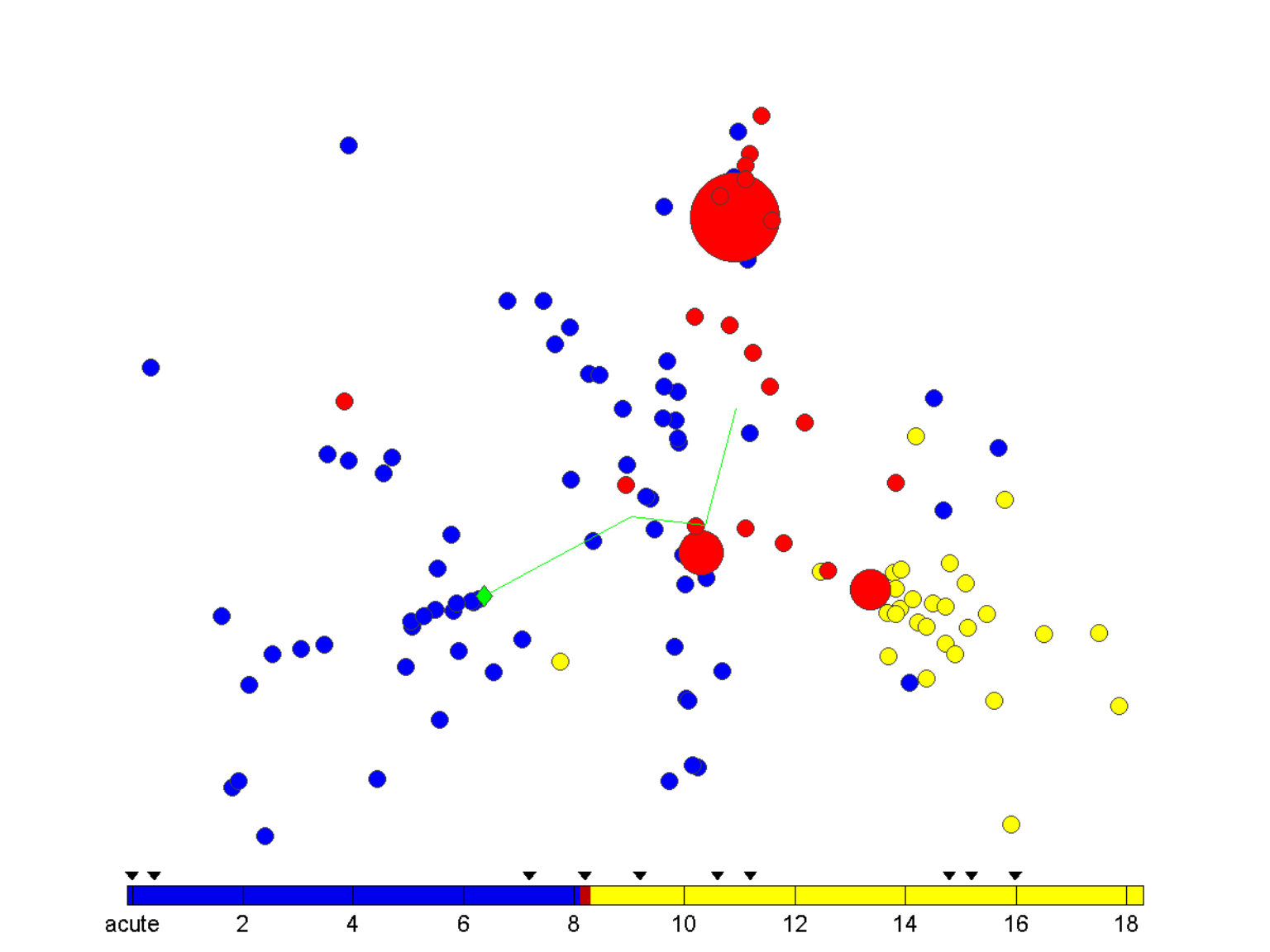
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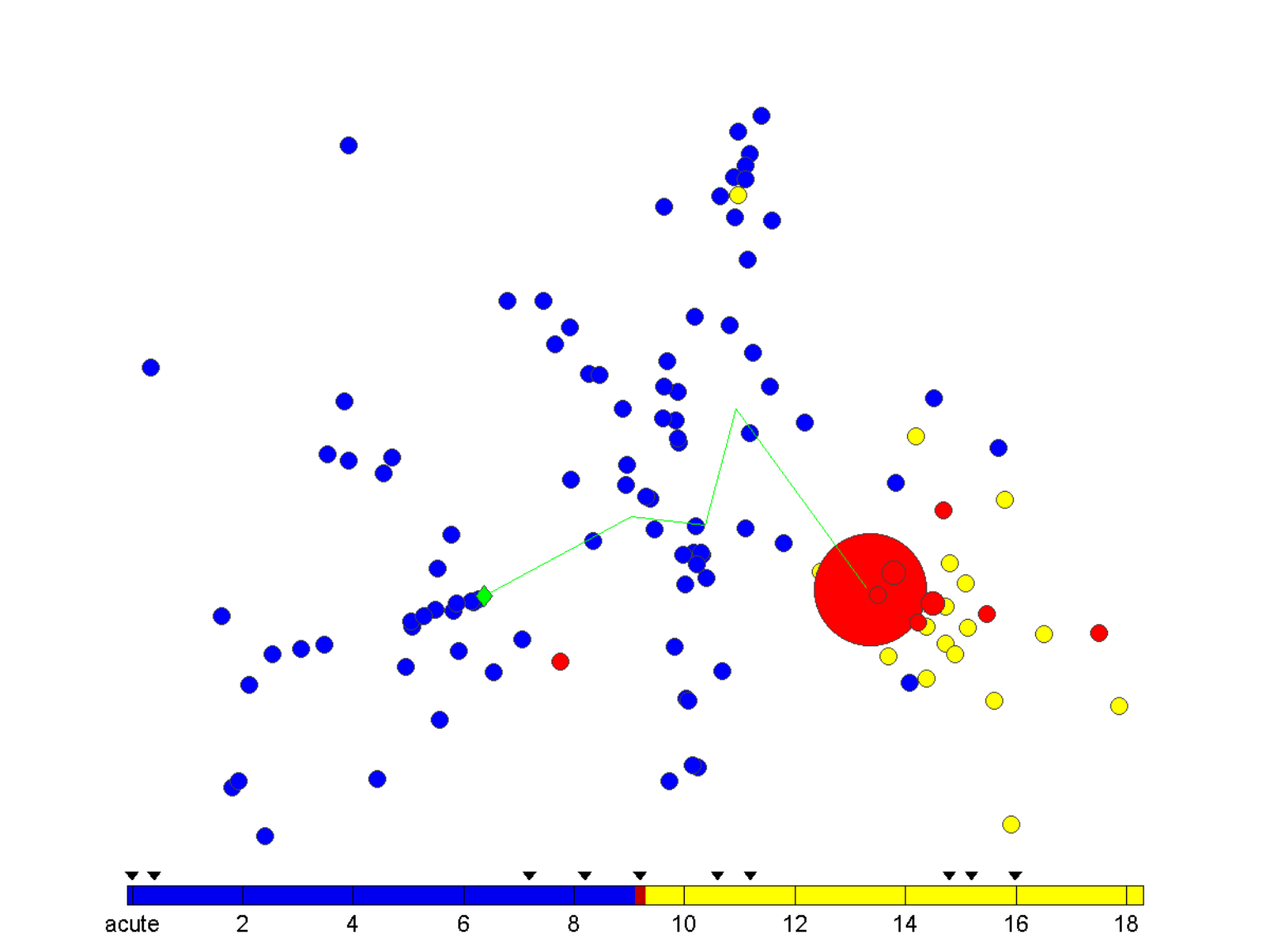
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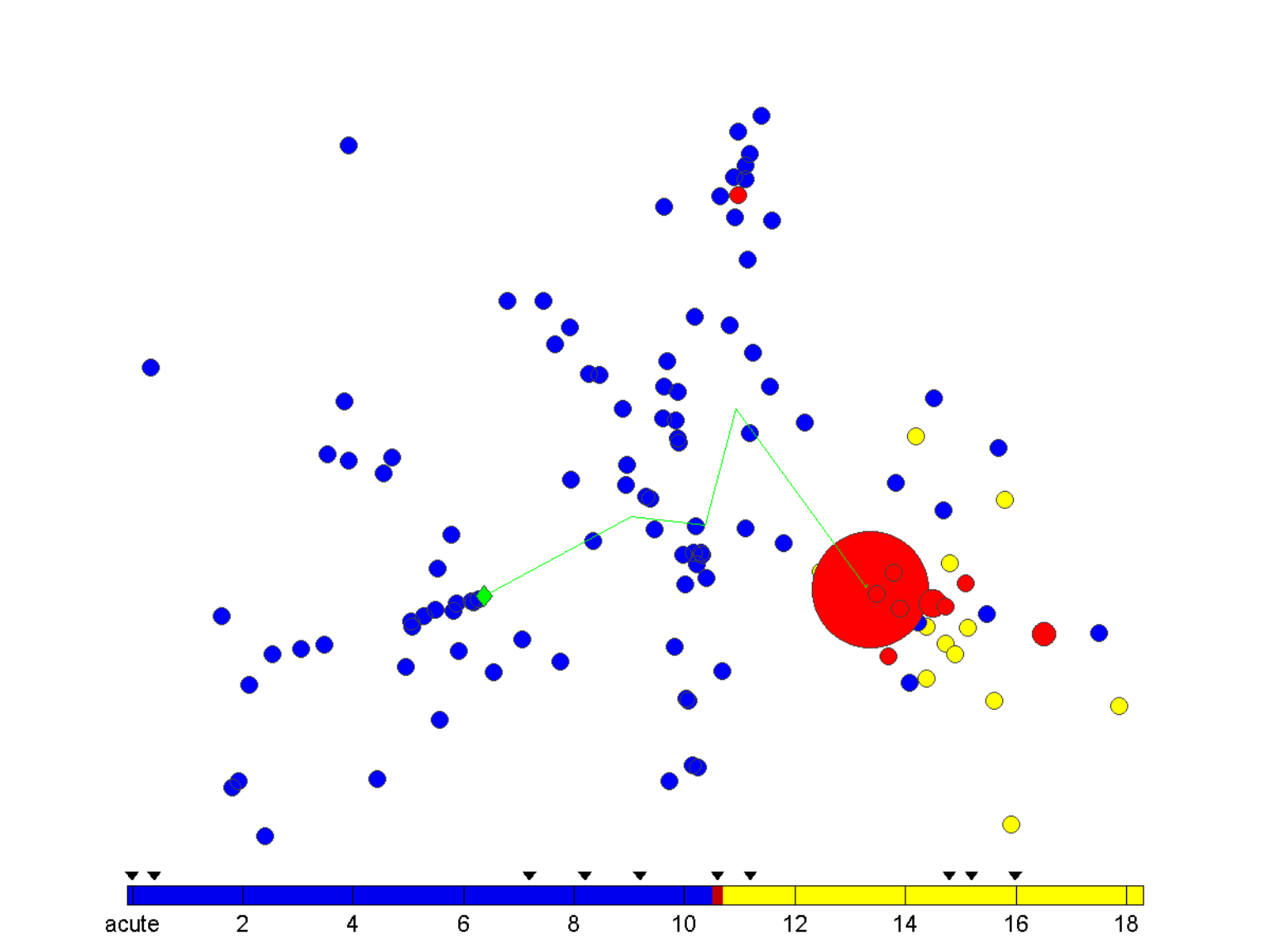
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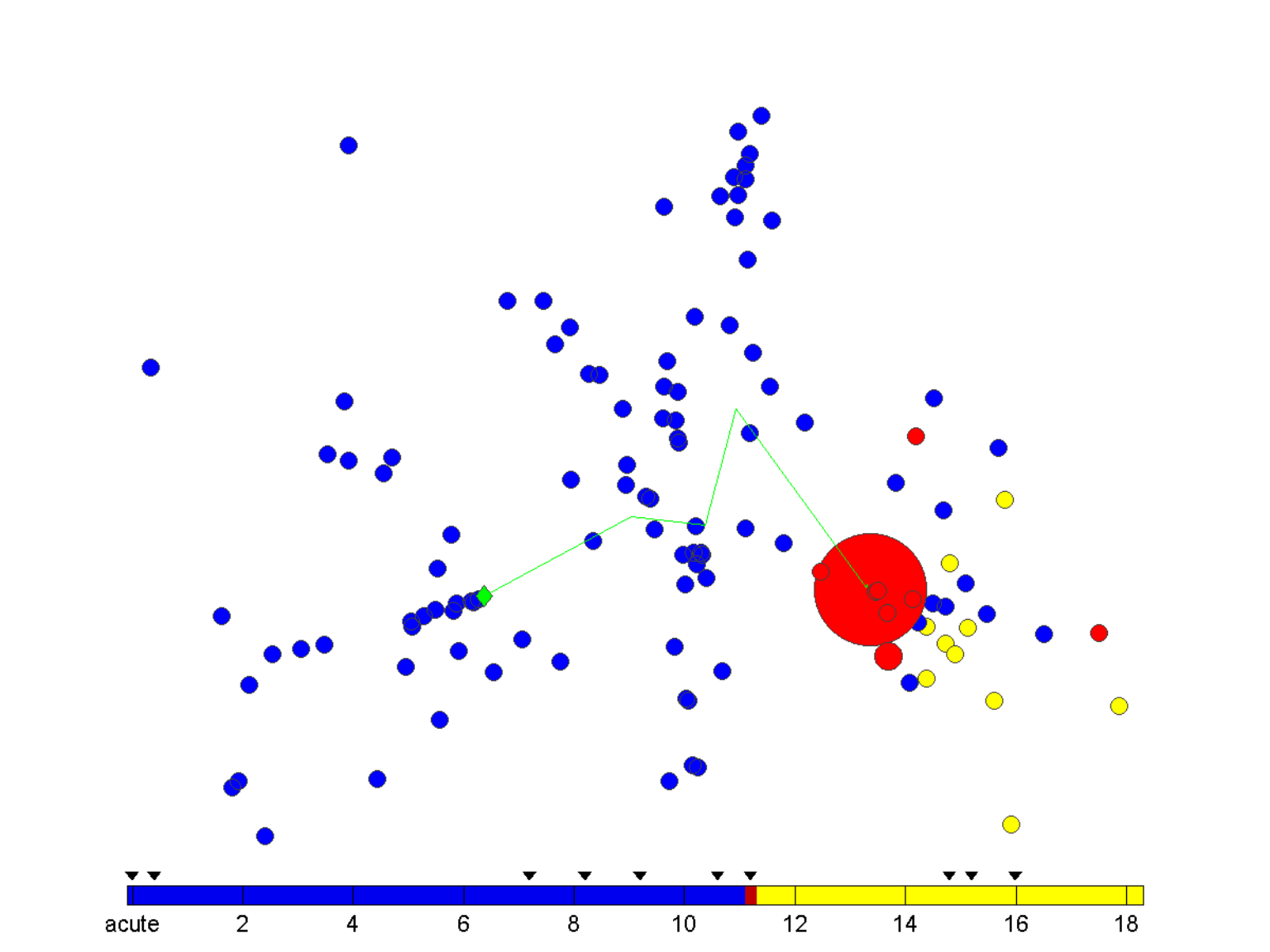
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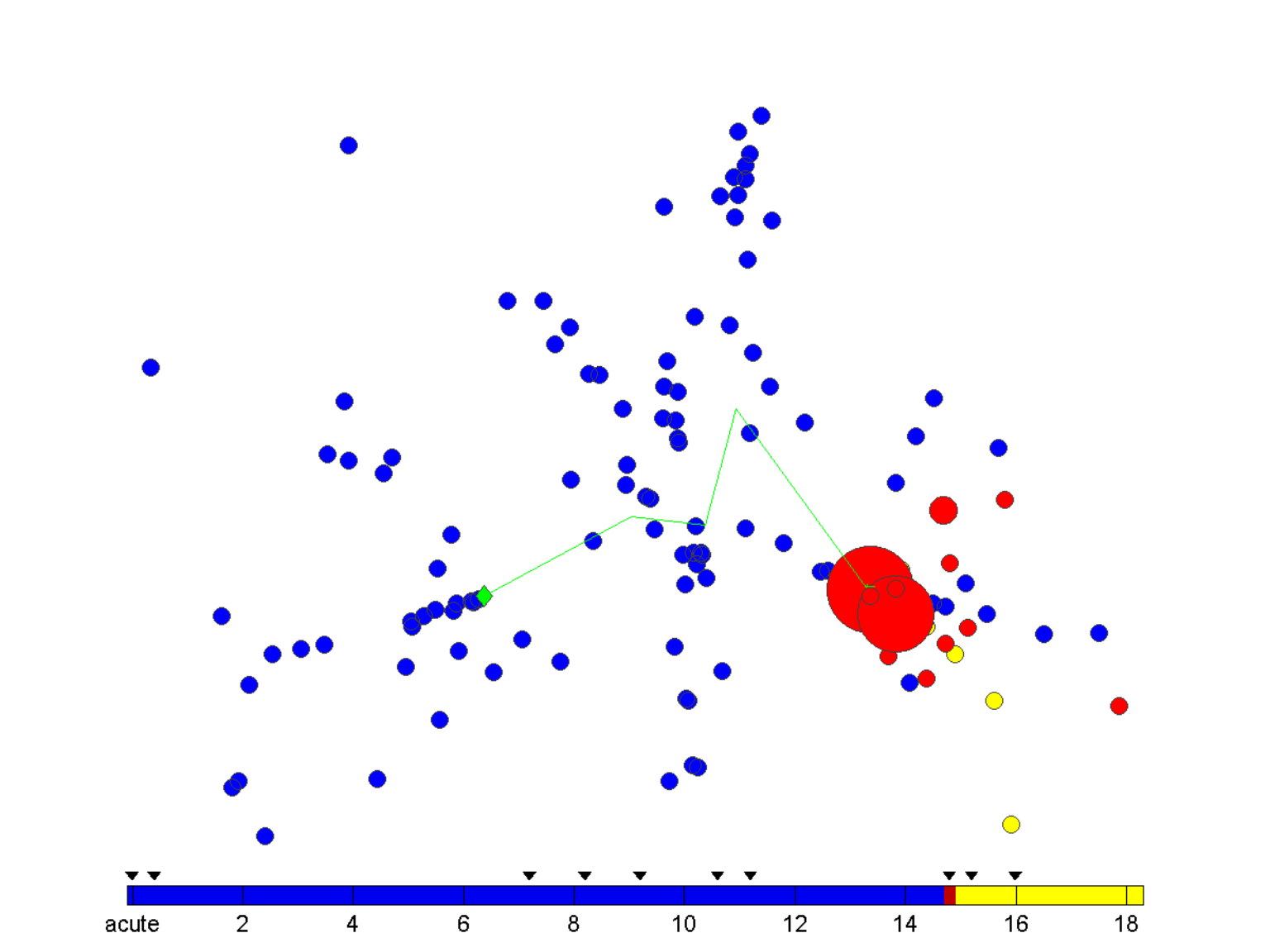
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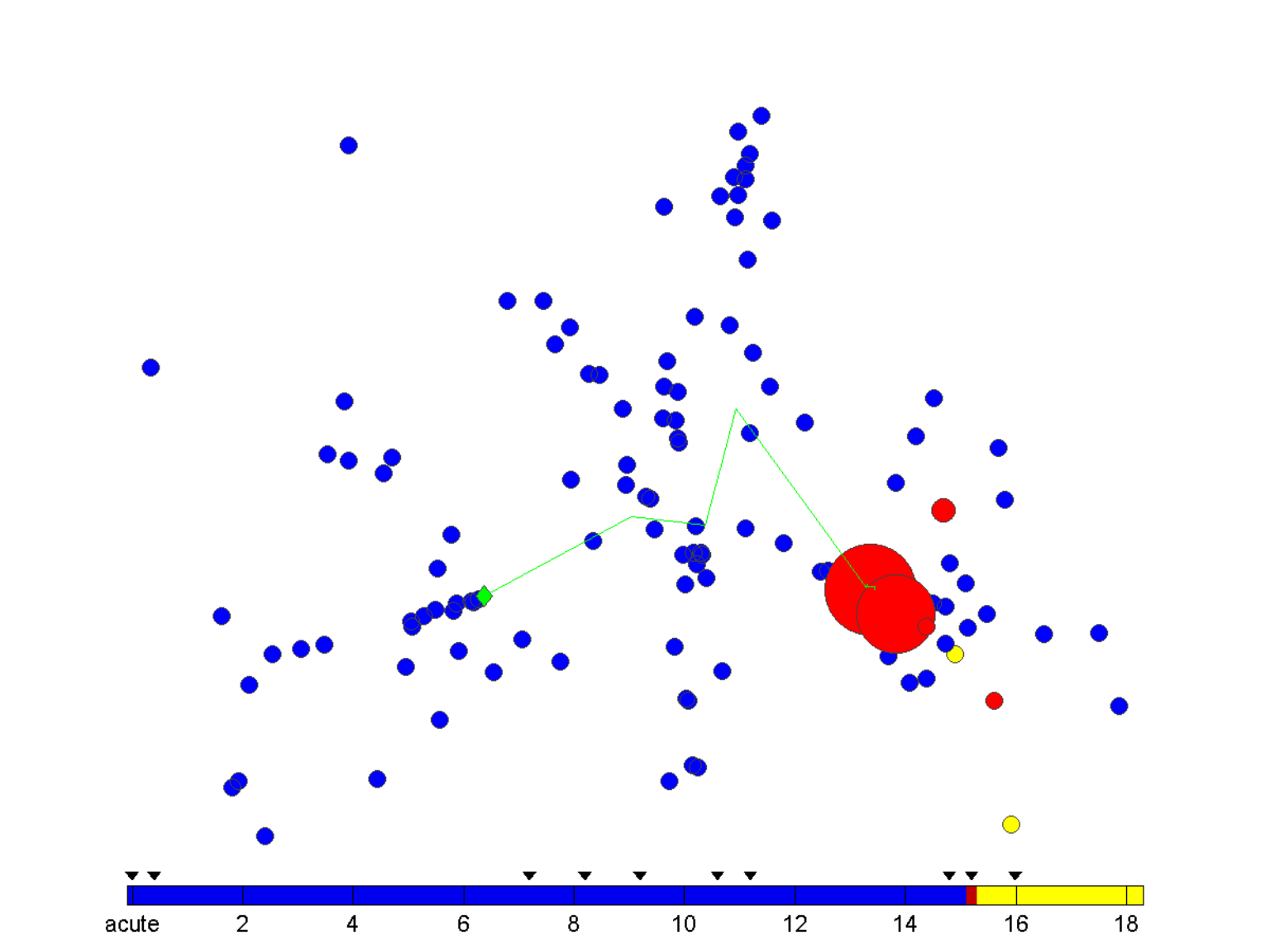
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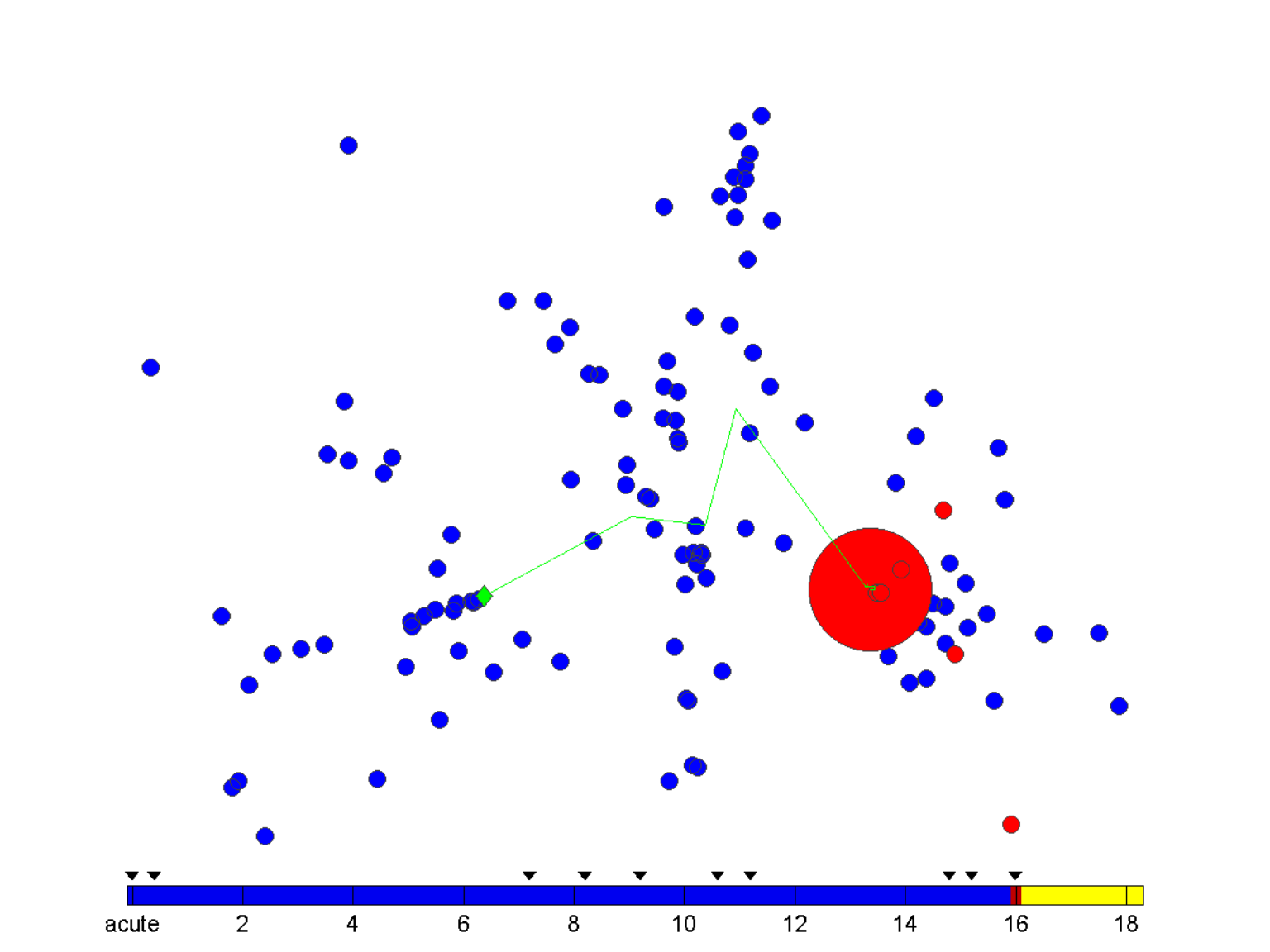
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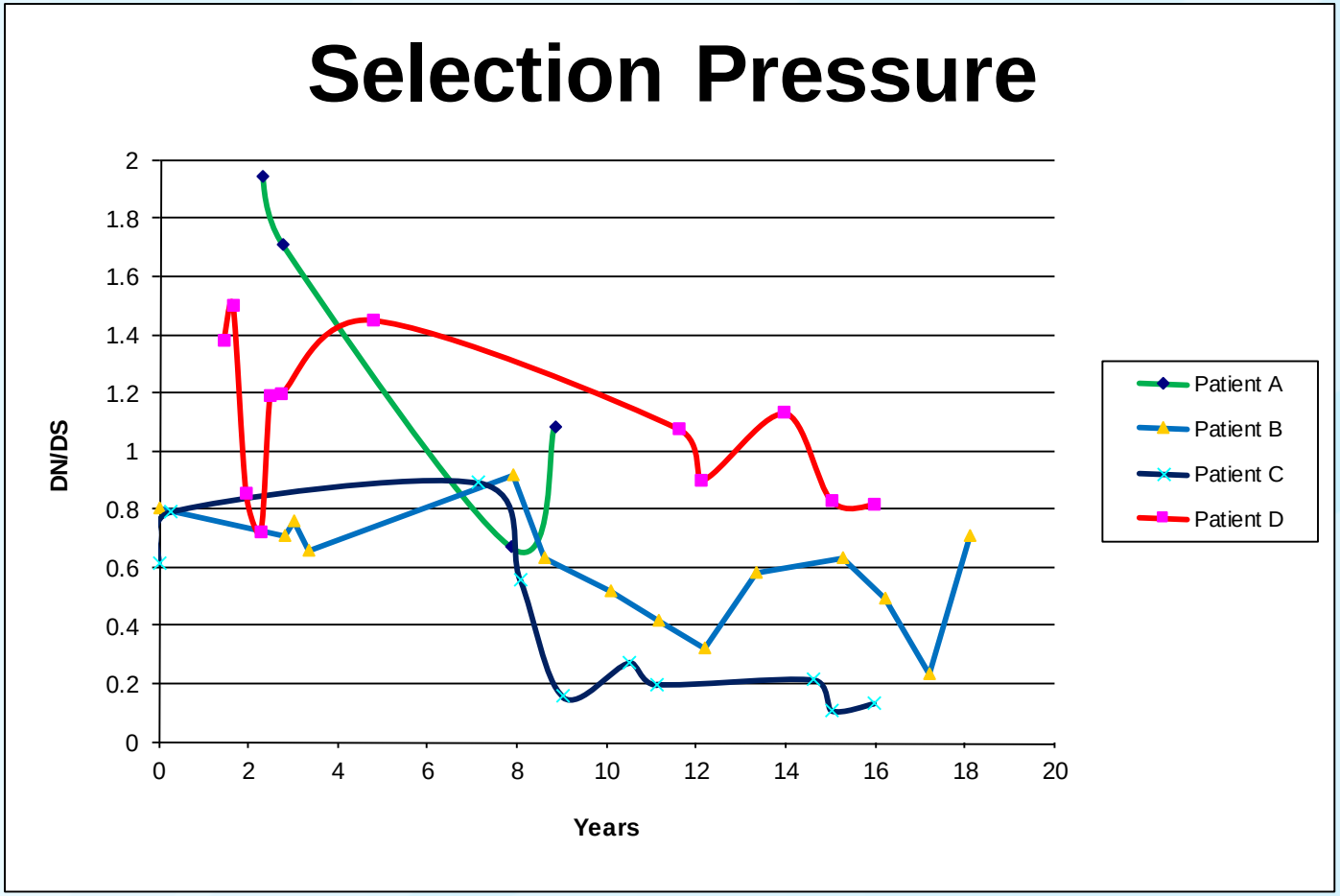


Strong negative selection is observed for ~74% of chronically infected individuals (Campo et al., 2014)

Mathematical modelling

Mathematical model for HIV

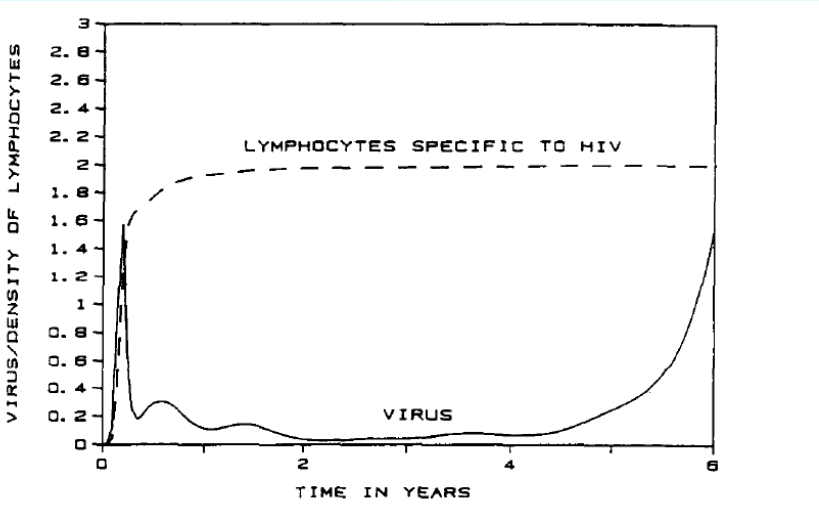
$$\dot{x}_i = x_i(f - sz - pr_i), \qquad i = 1, \dots, n$$

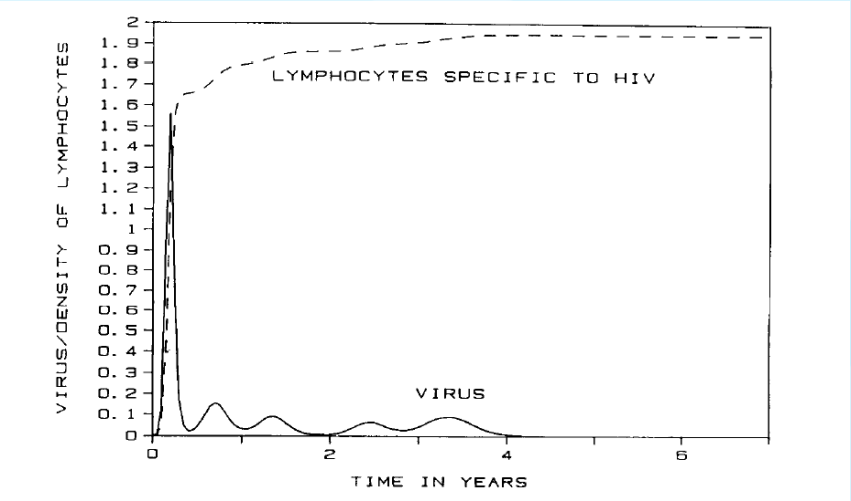
$$\dot{r}_i = cx_i - ux_i r_i, \qquad i = 1, \dots, n$$

$$\dot{z} = c' \sum_{i=1}^{n} x_i - u \sum_{i=1}^{n} x_i \, z, \qquad i = 1, \dots, n$$

- *n* viral variants
- x_i is the size of the population of the viral variant *i*;
- r_i is the i-specific immune response
- z – cross-immunoreactive response

Novak et al., Science, 1991; Math Biosci., 1991; AIDS, 1990





Novak et al., Math Biosci., 1991

Main prediction based on stationary solutions: viral adaptation is associated with increasing intra-host viral diversity

HCV model: Wodarz D et al, 2003

- *n* viral variants
- x is the number of uninfected hepatocytes (liver cells)
- y_i is the number of hepatocytes infected by the viral variant *i*;
- v_i is the size of the population of the viral variant *i*;
- w_i is the i-specific immune response
- z – cross-immunoreactive response

$$\dot{x} = \lambda - dx - \beta x \sum_{i=1}^{n} v_i$$

$$\dot{y}_i = \beta x v_i - a y_i - p y_i z$$

$$\dot{v}_i = k y_i - u v_i - q v_i w_i$$

$$\dot{w}_i = g v_i w_i - h w_i$$

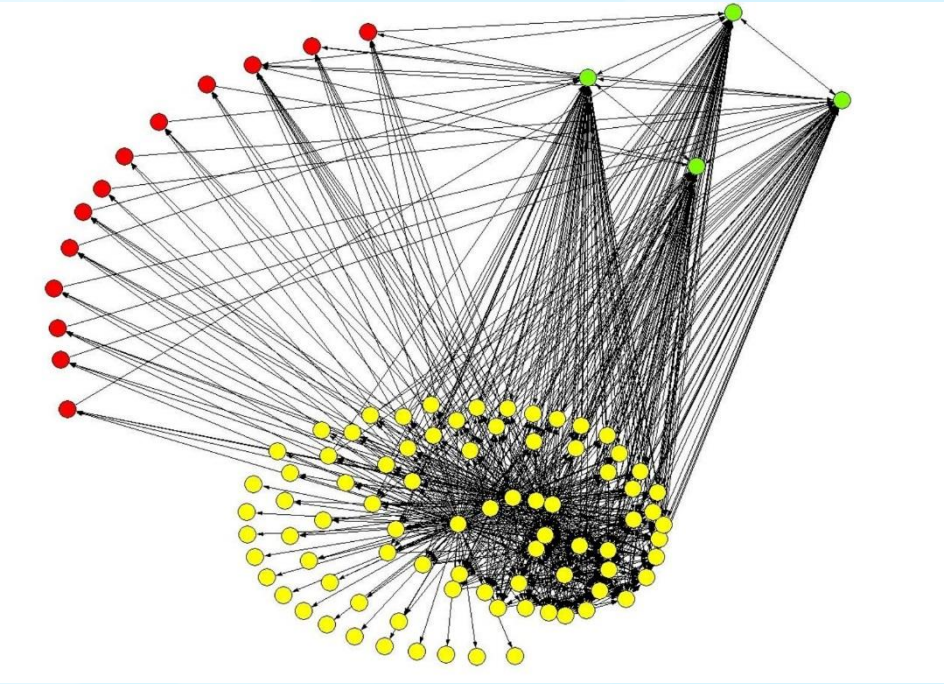
$$\dot{z} = cz \sum_{i=1}^{n} y_i - bz$$

Main prediction: similarly to HIV, viral adaptation is associated with increasing intra-host viral diversity

Mathematical model

Main assumptions:

- Complex cross-immunoreactivity network



- Disparity between immune activation and neutralization

Both assumptions were experimentally observed

Mathematical model

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = f x_i - p\left(r_i + \sum_j \beta_{j,i} r_j\right) x_i, \qquad i = 1, \ldots, n$$

$$\frac{\mathrm{d}r_i}{\mathrm{d}t} = c\left(\sum_j \frac{\alpha_{ji} r_i}{\sum_k \alpha_{jk} r_k} x_j\right) - b r_i, \qquad i = 1, \ldots, n$$

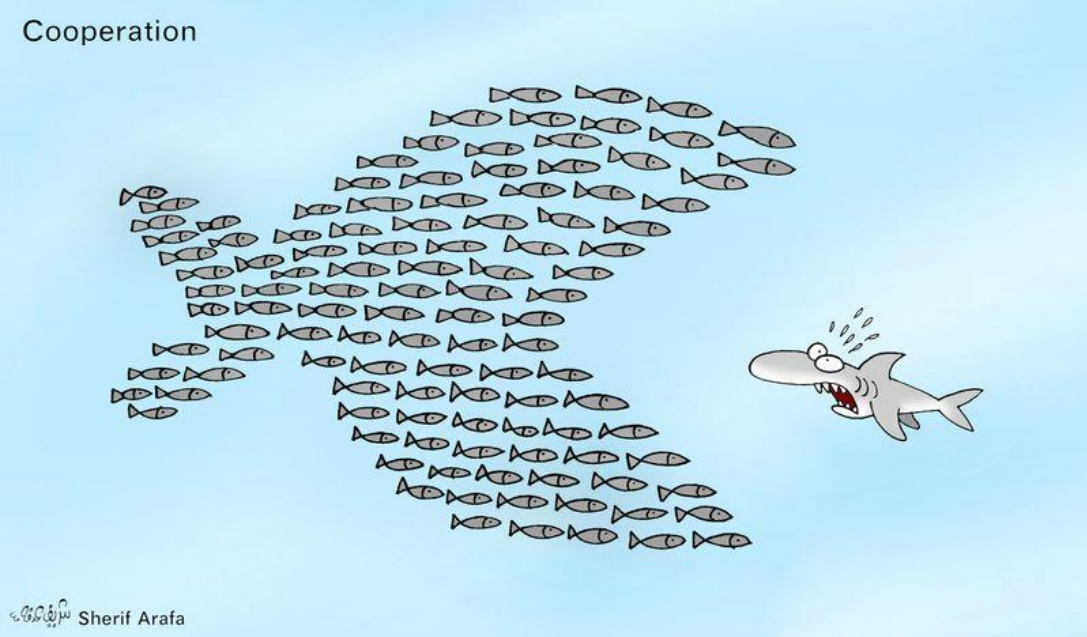
- x_i is the size of the population of the viral variant *i*;
- r_i is the i-specific immune response
- *f* – viral replication rate; *p* - immune response strength
- *c* – immune response rate; *b* – immune response decay rate
- *A*,*B* – cross-immunoreactivity stimulation and neutralization matrices. In particular, we may assume that $A = \alpha M$, $B = \beta M^T$, where *M* is an adjacency matrix of CRN

Model predictions

1. **Antigenic cooperation**

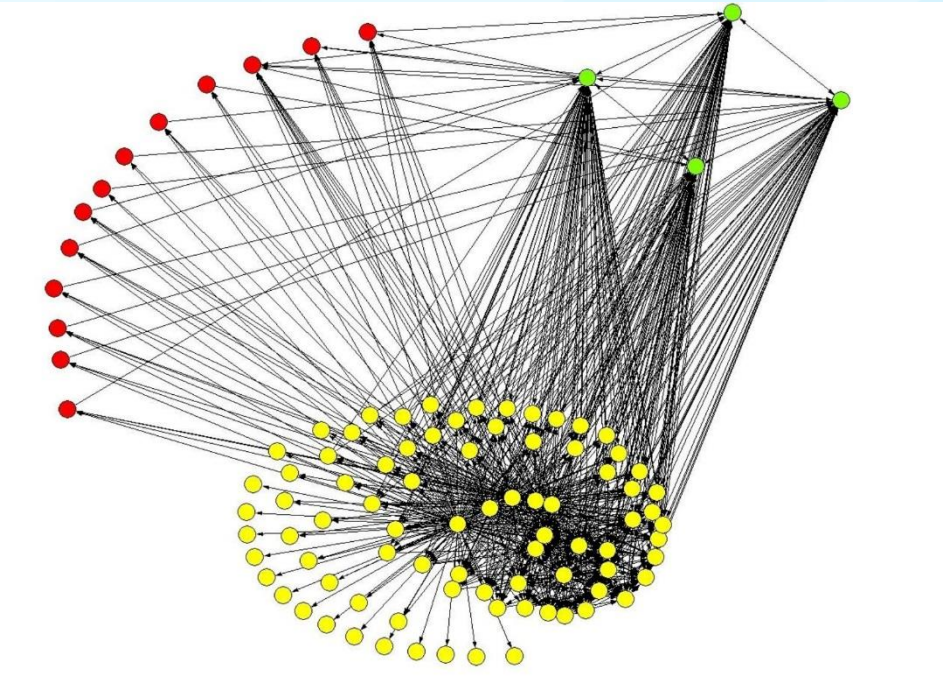
Antigenic cooperation

- The members of HCV intra-host populations don't act like separate entities; the different variants work together almost like a team with a clear separation of responsibilities
- Roles of variants are determined by their positions in cross-immunoreactivity network (CRN)



Antigenic cooperation

- **Altruistic variants:** sacrifice themselves for the good of the whole population. They draw the immune system attack on themselves. Those variants are in-hubs in CRN
- **Selfish variants:** gain fitness at the expense of altruists. Remain in existence without eliciting strong specific immune responses and persist under negative selection. Those variants are adjacent to altruists

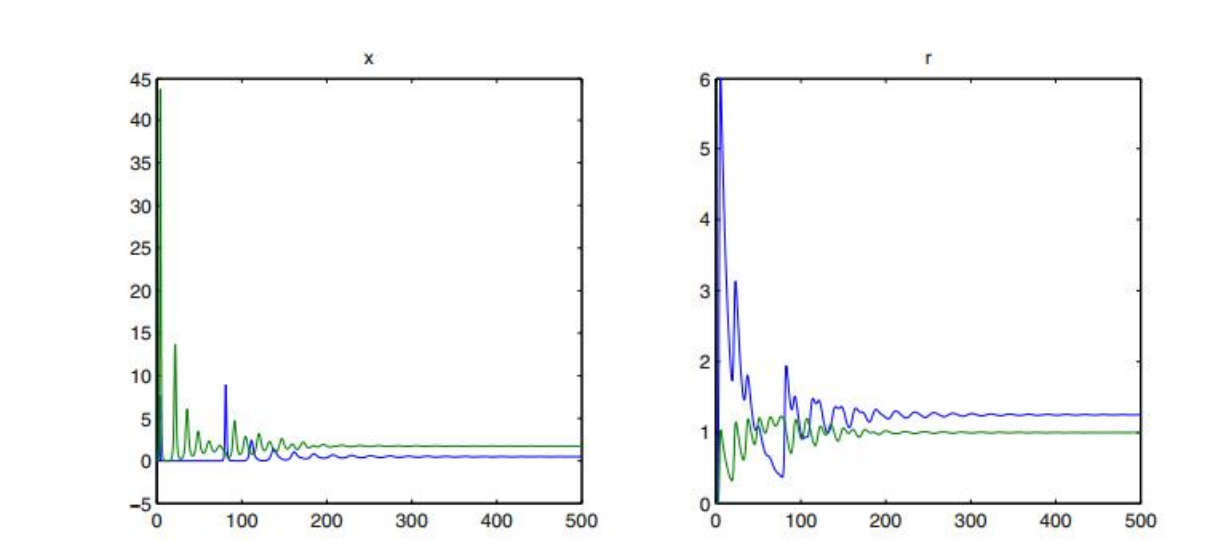


Example: 2 viral variants. Variant 2 is able to interact with Variant 1 as both immunogen and antigen with certain affinities ($0 < \beta < \alpha < 1$).

Stable stationary solution:

$$\left(\frac{b(1-\alpha)f_1}{cp}, \frac{b(f_2+(\alpha-\beta)f_1)}{cp}, \frac{f_1}{p}, \frac{f_2-\beta f_1}{p}\right)$$

Variant 2 achieves higher equilibrium population size by utilizing replicative abilities of both itself and Variant 1



- Variants with low replicative fitness and broad cross-immunoreactivity can outcompete the high-fitness variants.
- Low fitness and small initial population size are essential for persistence

Model predictions

1. Antigenic cooperation
2. **Remote interactions of viral variants and populations fluctuations**

Remote interactions between viral variants

$s^* = (x_1^*, \dots, x_n^*, r_1^*, \dots, r_n^*)$ – stable equilibrium solution of (1)-(2)

Then s^* is a solution of the following system of linear equations:

$$\sum_{j=1}^{n} \beta_{j,i} r_j^* = \frac{f_i}{p}, \qquad i \in I_2$$

$$\sum_{j=1}^{n} \frac{\alpha_{ji}}{\sum_{k=1}^{n} \alpha_{jk} r_k^*} x_j^* = \frac{b}{c}, \qquad i \in J_2$$

$$I_1 = \left\{ i \in [n] : f_i - \sum_{j=1}^{n} \beta_{j,i} r_j^* \neq 0 \right\}, I_2 = [n] \backslash I_1$$

$$J_1 = \{ i \in [n] : r_i^* = 0 \}, J_2 = [n] \backslash J_1$$

Remote interactions between viral variants

Assume that B = E and $f_i = f$, i=1,…,n. Then for all $i \in I_2$ we have

$$r_i = \frac{f}{p}$$

and

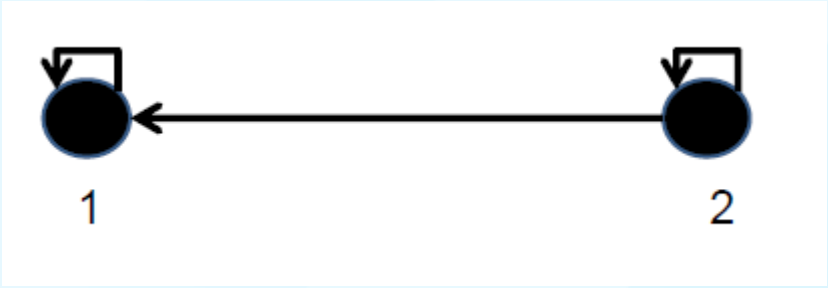
$J_1 = \emptyset$ (if $i \in J_1$, then f is an eigenvalue of the Jacobian of (1)-(2)

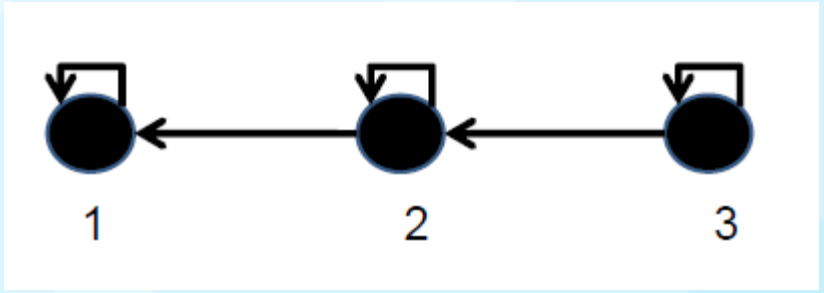
Remote interactions between viral variants

$$\sum_{j=1}^{n} \frac{\alpha_{ji}}{\sum_{k=1}^{n} \alpha_{jk}} x_j^* = \frac{bf}{cp}, \qquad i \in [n]$$

$$\mathrm{D}x^* = \mathbf{1}$$

Example





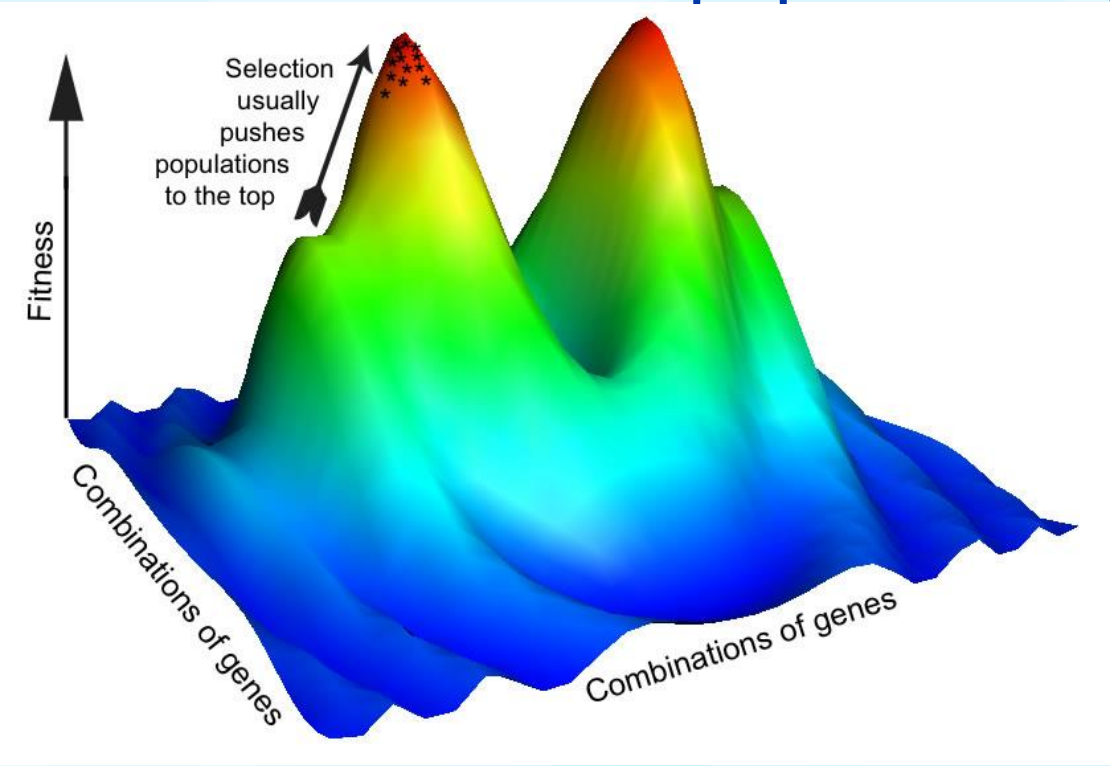
$$\delta_1 x_1 + \delta_2 x_2 = 1$$
$$\delta_2 x_2 = 1$$

$$x_1 = 0, x_2 = {}^{1}/_{\delta_2}$$

$$\delta_1 x_1 + \delta_2 x_2 = 1$$
$$\delta_2 x_2 + \delta_3 x_3 = 1$$
$$\delta_3 x_3 = 1$$

$$x_1 = {}^{1}/_{\delta_1}, x_2 = 0, x_3 = {}^{1}/_{\delta_3}$$

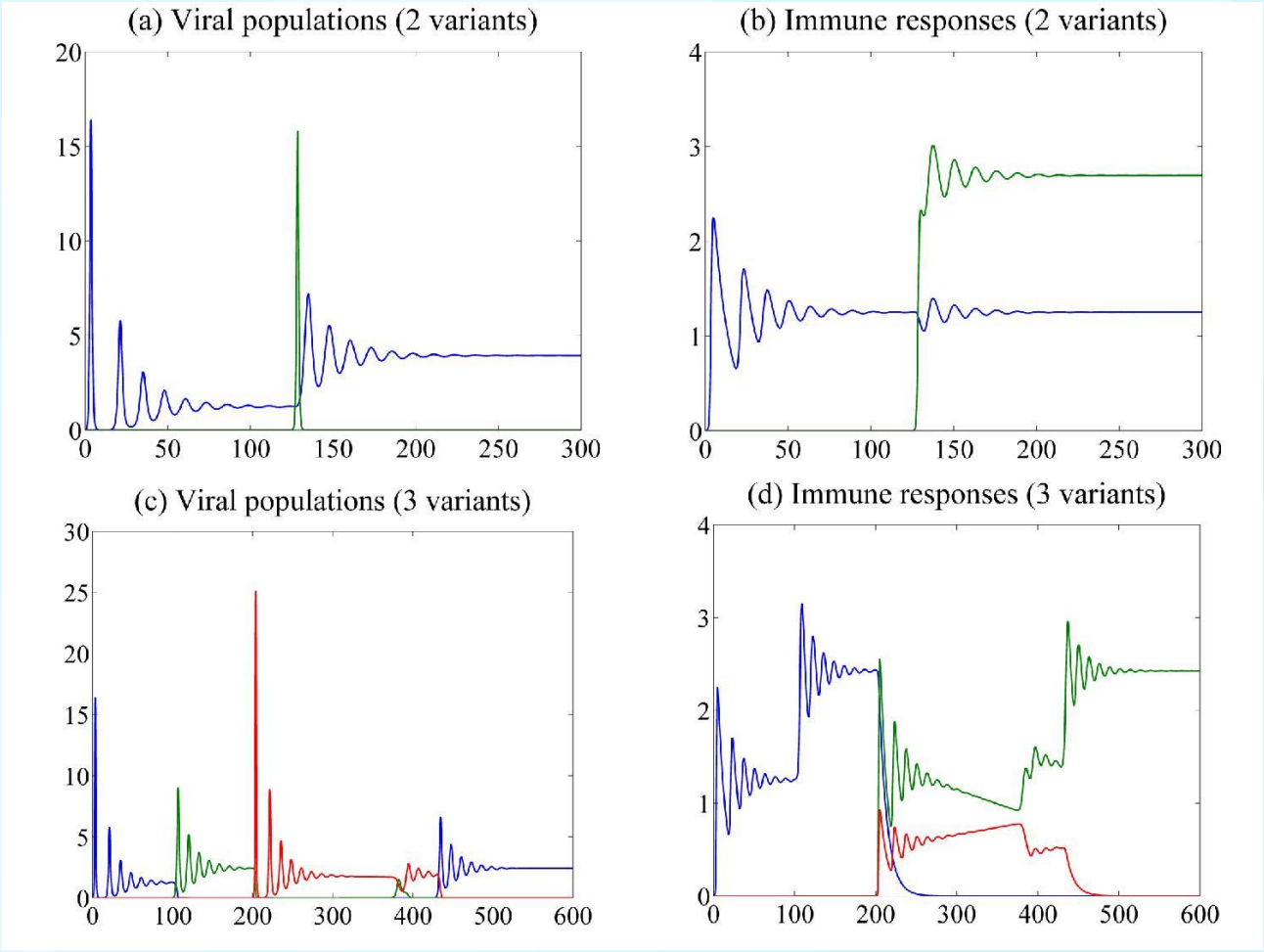
Remote interactions and population dynamics



http://evolutionarysystemsbiology.org

- Fitness landscape is **dynamic**
- Each viral variant influence fitness landscape within the same component of CRN

Remote interactions and population dynamics



Conclusions

- Antigenic cooperation (AC) explains intra-host adaptation of HCV

- Indirect interactions in CRN and AC explain complex dynamics of HCV intra-host populations

- Interference with AC is a potential strategy for interruption and prevention of chronic HCV infection

Thank you!

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