

Supplementary Digital Content 1

Viral Load Criteria and Threshold Optimization to Improve HIV Incidence Assay Characteristics - A CEPHIA Analysis

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Calculation of Context-Specific False-Recent Rate

Formal Definition

The **false-recent rate**, ε_T , is the probability that a randomly selected subject who is infected for longer than T will return a ‘recent’ result.

Therefore,

$$\varepsilon_T = \int_T^{\infty} f(t)P_R(t) dt \quad (1)$$

where

- $f(\cdot)$ is the probability density function for time since infection in the long-infected population (at the time of the incidence study), and
- $P_R(t)$ is the probability that a subject is in the ‘recent’ state a time t after infection.

The density $f(t)$ will depend on the full demographic and epidemiological history of the population. For an incidence survey performed at time 0, assuming that the post-infection survival dynamics remain unchanged over time, $f(t)$ can be expressed as a function of incidence, population size and post-infection survival:

$$f(t) = \frac{I(-t)N_S(-t)P_A(t)}{\int_T^{\infty} I(-u)N_S(-u)P_A(u) du} \quad (2)$$

where

- $I(u)$ is the incidence at time u ,
- $N_S(u)$ is the susceptible population size at time u , and
- $P_A(u)$ is the probability of still being alive at time u after infection (i.e. being alive at the time of the survey, given that infection occurred time u into the past).

If the long-infected population can be divided into k distinct subpopulations, within each of which the recent infection testing algorithm (RITA) produces a distinct function $P_R(t)$, then

$$\varepsilon_T = \sum_{i=1}^k P_i \int_T^{\infty} f_i(t)P_{R,i}(t) dt \quad (3)$$

where

- P_i is the prevalence of individuals in subpopulation i amongst all long-infected individuals ($i = 1, 2, \dots, k$),
- $f_i(t)$ is the density function for times since infection amongst long-infected individuals in subpopulation i ,
- $P_{R,i}(t)$ is the probability that a subject in subpopulation i is in the ‘recent’ state a time t after infection.

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Simplified Formulation

To demonstrate the context dependence of the False-Recent Rate (FRR), the following simplified formulation of Equation (3) was used in this work:

$$\varepsilon_T = c \cdot P_{R,tx} + (1 - c) \cdot \int_T^{\infty} f(t)P_R(t) dt \quad (4)$$

where

- c is the treatment coverage, or the percentage of the long-infected population on treatment,
- $P_{R,tx}$ is the FRR in the *treated* long-infected population,
- $f(\cdot)$ is the probability density function for time since infection in the *untreated* long-infected population, and
- $P_R(t)$ is the probability that an *untreated* subject is in the ‘recent’ state a time t after infection.

The value of $P_{R,tx}$ and the function $P_R(\cdot)$ depend on the specific RITA that is utilized and its behavior in the population of interest; while treatment coverage c and the density $f(\cdot)$ depend only on characteristics and history of the population.

In this analysis, the following form for $f(\cdot)$ was chosen:

$$f(t) = \begin{cases} \frac{g(t)}{\int_T^{\infty} g(u) du} & \text{if } t > T \\ 0 & \text{elsewhere} \end{cases} \quad (5)$$

where $g(t) = \exp\left(-\left(\frac{t}{a}\right)^b\right)$.

One could consider $g(\cdot)$ as giving the general form of the distribution of time since infection in the entire untreated population¹, which is then vertically scaled and truncated to describe only the long-infected population by the probability density function $f(\cdot)$. In the special case of epidemiological and demographic equilibrium, $g(t)$ equals the survival function $P_A(t)$ in see Equation (2).

A value for the shape parameter b of 4.5 was used in this analysis, and was chosen somewhat arbitrarily to produce a density that neither has a very long tail nor steps down from relatively high values to zero very sharply. The value of the scale parameter a was chosen to provide a specified average time since infection in the long-infected population, denoted by m .

¹ Although $g(\cdot)$ is not theoretically a probability density function

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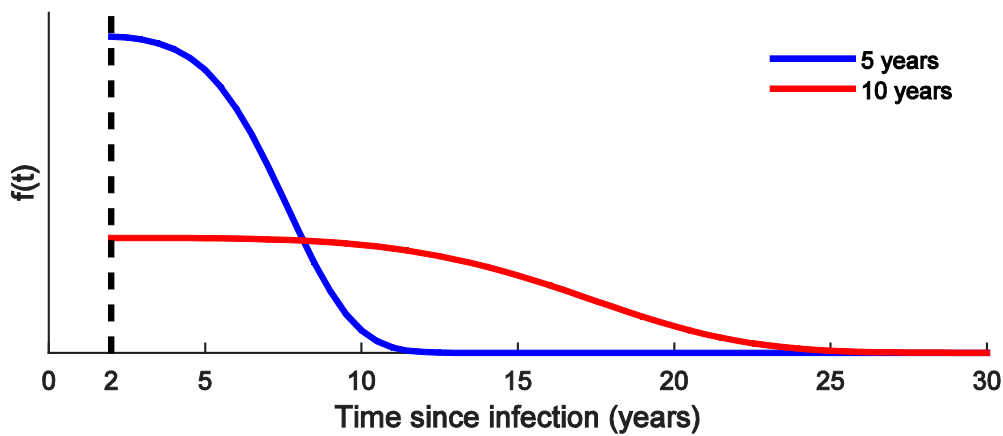
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Note that several aspects of the population influence the mean time since infection m . For example, a small value of m may result from: (i) high treatment coverage which results in subjects remaining untreated for only short periods post infection, (ii) HIV infections only beginning to occur in the population a few years before the incidence survey and therefore no subjects who have been infected for several years, or (iii) healthcare and knowledge in the population being poor, resulting in subjects dying soon after infection. The detailed construction of the distribution of ‘time since infection’ is therefore nuanced, and therefore should be approached differently from one scenario to another.

Inputs

The **external inputs** to the FRR calculation, and the values used, are:

- **Treatment coverage c :** 0%, 20%, 50%, 80%.
- **Mean time since infection m :** 5 years, 10 years. These correspond to values of a of 7.3685 and 16.8078 respectively. The resulting density function $f(t)$ is shown for $T = 2$ years.



The **CEPHIA data** was used to inform $P_{R,tx}$ and $P_R(t)$:

- The percent of long-infected treated subjects that were classified as ‘recently’ infected was used as a *proxy* for $P_{R,tx}$. In all of the hypothetical scenarios considered, there is no early treatment and therefore only data on subjects who initiated treatment more than 2 years after infection was used to estimate $P_{R,tx}$.
- The function $P_R(t)$ was estimated by fitting a logistic regression model to the RITA classifications for subjects who had never been on treatment and were not SCOPE elite controllers. The regression model was of the form

$$\log\left(\frac{P_R(t)}{1 - P_R(t)}\right) = \alpha_0 + \alpha_1 \cdot t + \alpha_2 \cdot t^2 + \alpha_3 \cdot t^3 \quad (6)$$

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and the parameters α_j , $j = 0,1,2,3$, were estimated by the method of maximum likelihood.

Data on subjects who have been infected for many years was scarce: amongst the 1 388 data points used in the estimation, providing classifications for 423 subjects at different (estimated) times post infection, the median (50th percentile) of time since infection is 1.1 years and the third quartile (75th percentile) is 2.2 years. The largest 5% of times lie between 3.9 years and 12 years.

The inputs $P_{R,tx}$ and $P_R(t)$ depend on the **specific RITA**. In this analysis, the following parameters are used to fully specify the RITA that is constructed from a chosen incidence assay: The **incidence immunoassay (IA) threshold**, the **viral load (VL) threshold**, and the **post-infection time cut-off T** . The cut-off T equals 2 year. A large number of IA thresholds were considered. The VL threshold was set to 0 (no viral load criteria), 75 or 1000 copies/ml.

The calculation of context-specific FRRs presented in this work is intended to demonstrate the importance and potential impact of context. In practice, uncertainties in all inputs should be propagated through the calculation to quantify the uncertainty in the estimated FRR, and the sensitivities to assumptions and the simplistic scenario construction assessed.

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Context-Specific False-Recent Rate as a Function of the Mean Duration of Recent Infection

The calculated context-specific FRRs are shown below, for each of the seven incidence assays (LAg, BED, Less-sensitive Vitros, Vitros Avidity, BioRad Avidity, Architect Avidity and Geenius) and a range of IA thresholds, for each combination of

- Treatment coverage c : 0%, 20%, 50%, 80%
- Mean time since infection m : 5 or 10 years
- VL threshold: 0, 75 or 1000 copies/ml

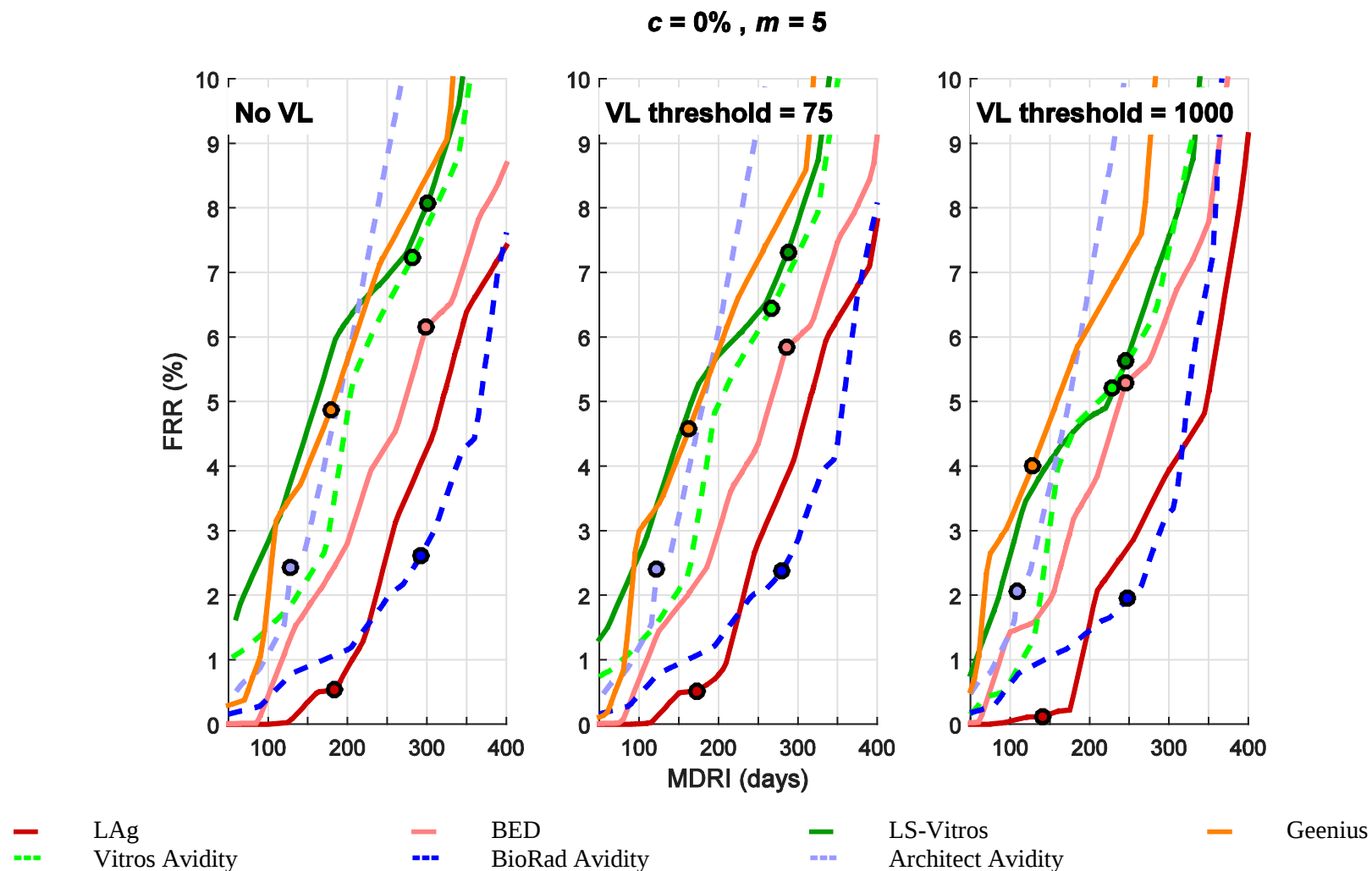
To allow for a more direct comparison of the incidence assays, the FRR is shown as a function of the Mean Duration of Recent Infection (MDRI) rather than IA threshold:

- For each incidence assay and choice of VL threshold, the IA threshold was chosen such that the desired MDRI was obtained (x-axis in figures).
- The corresponding context-specific FRR (y-axis) was then calculated for that RITA, based also on the specified c and m .

The circles indicate the RITA properties when the IA threshold is the current developer's proposed threshold.

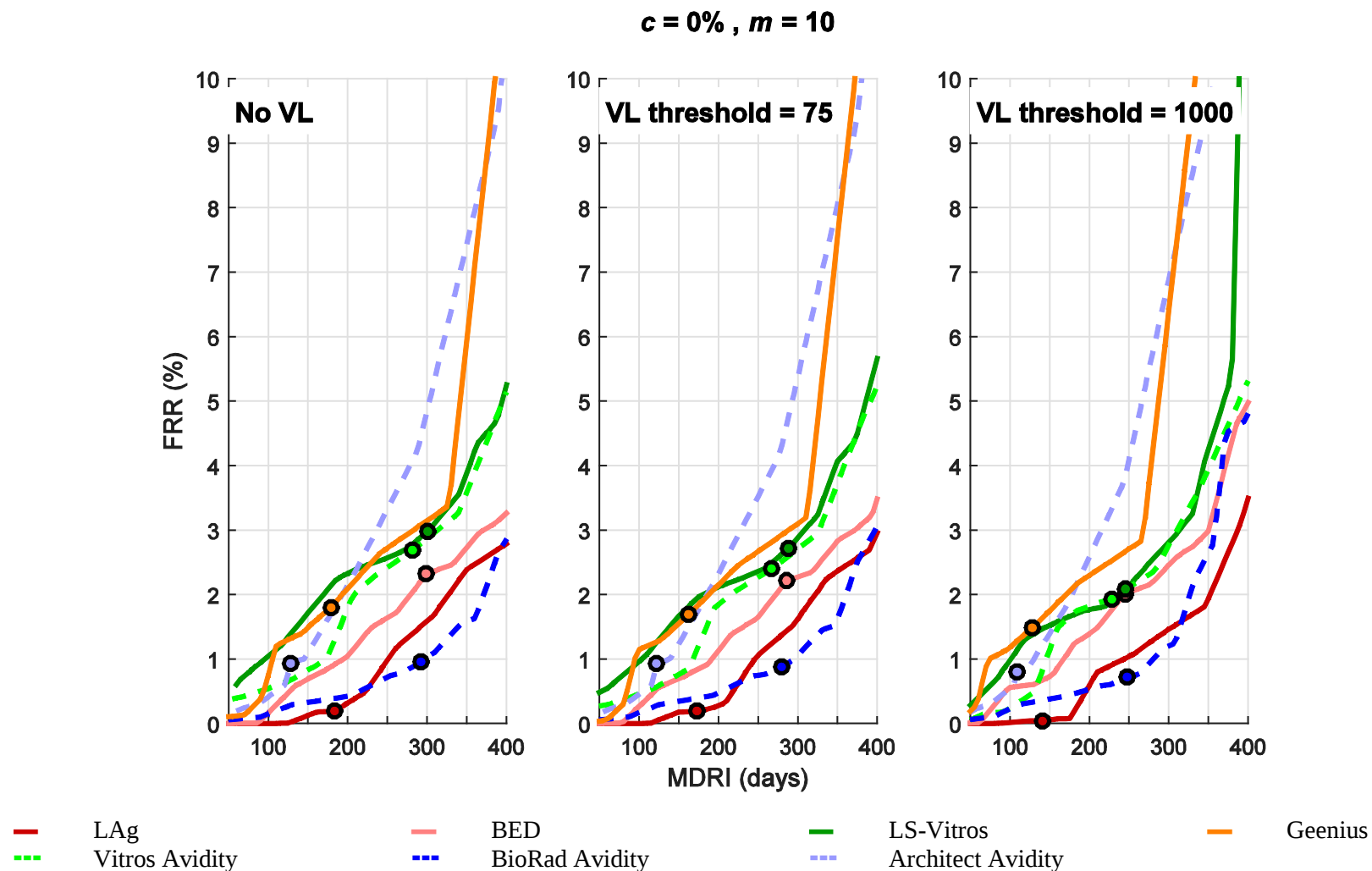
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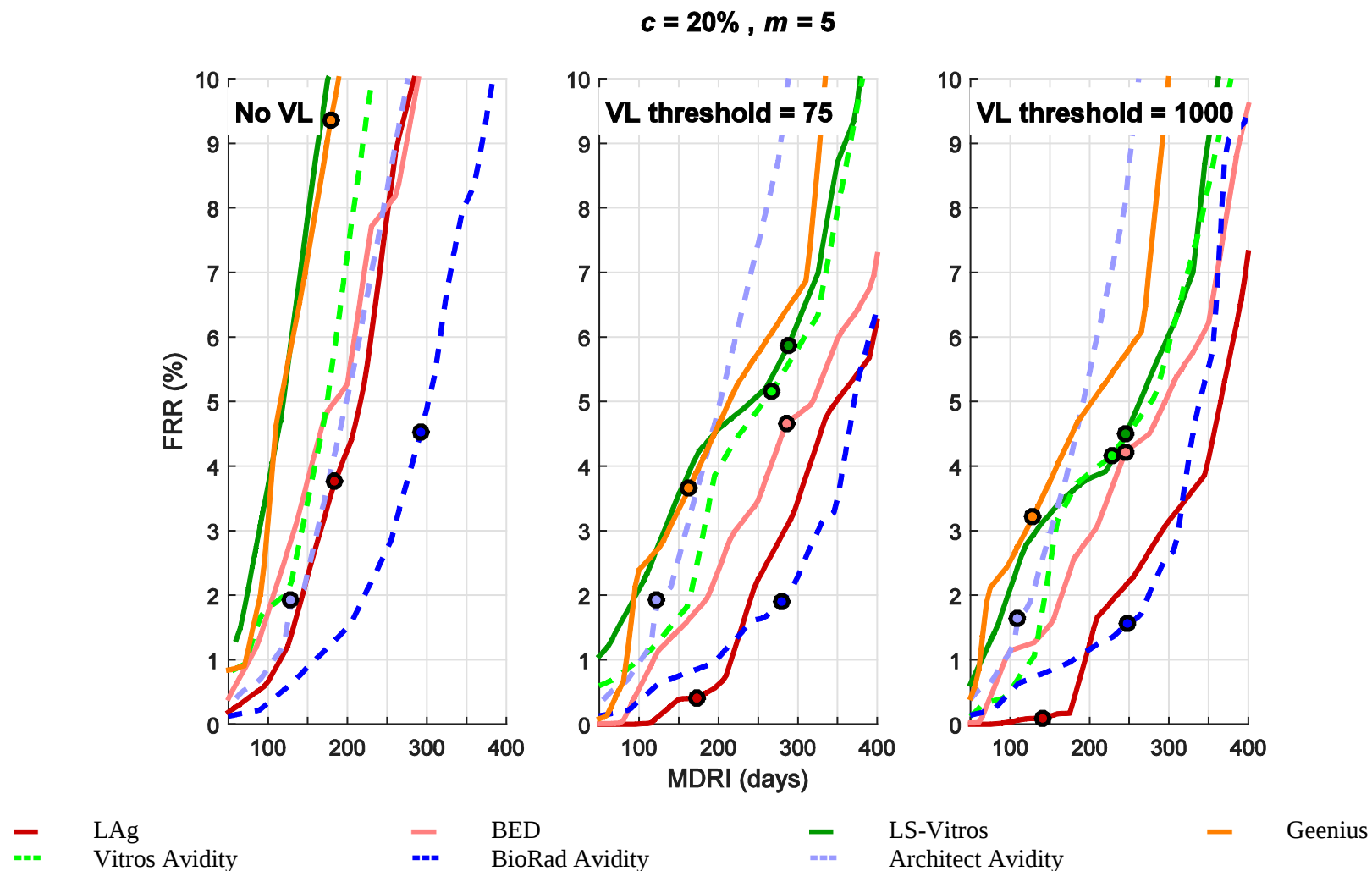
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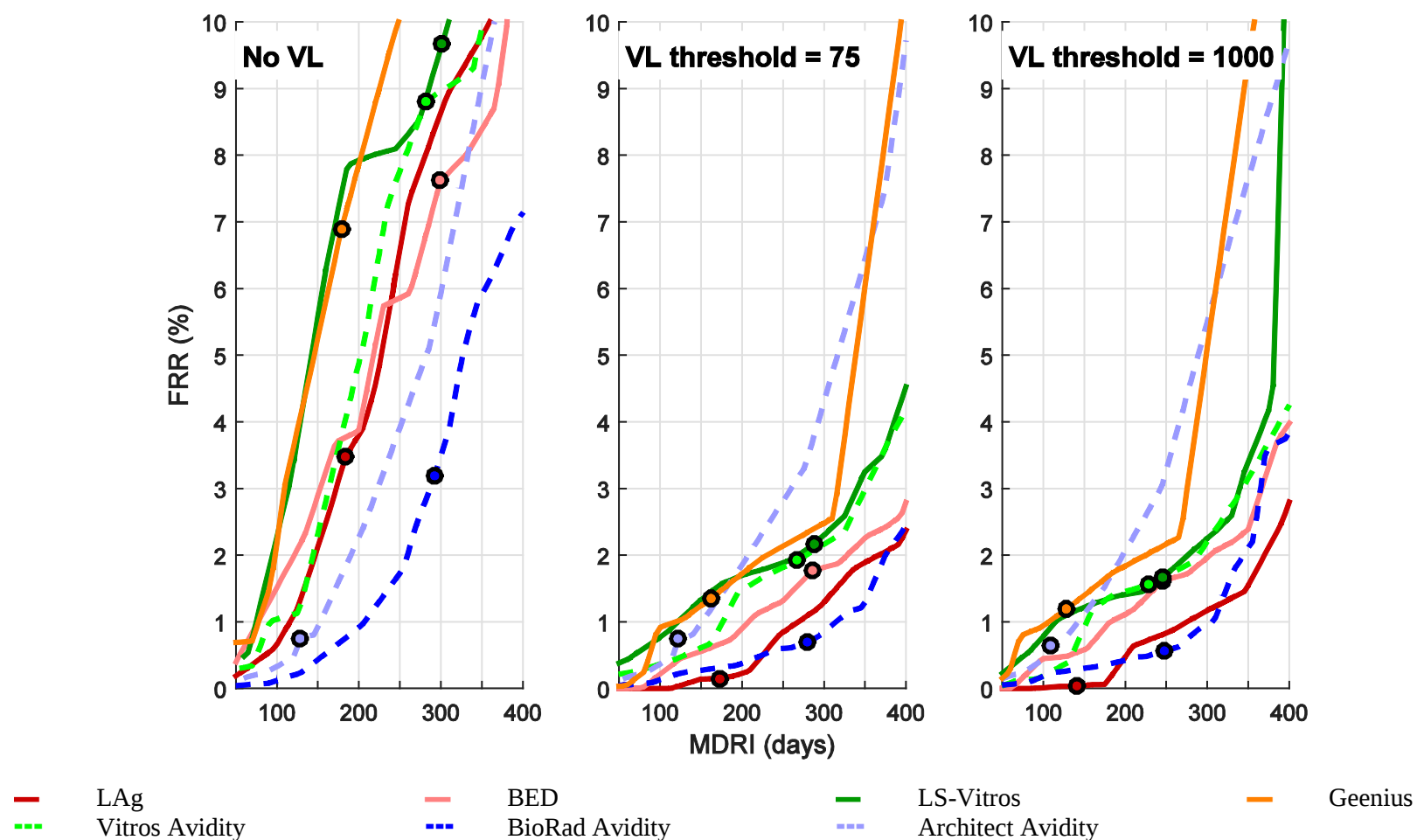
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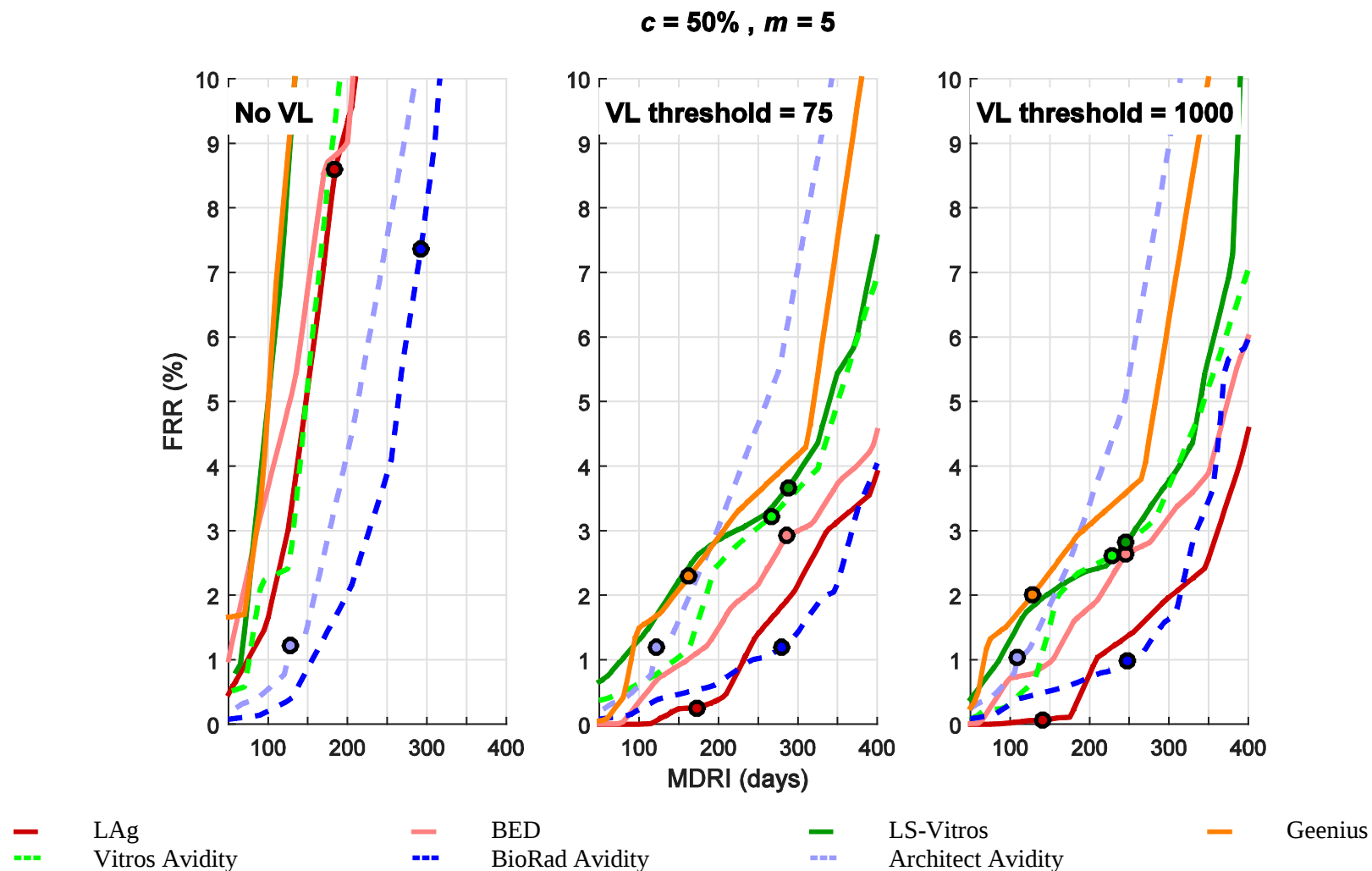
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$c = 20\%$, $m = 10$



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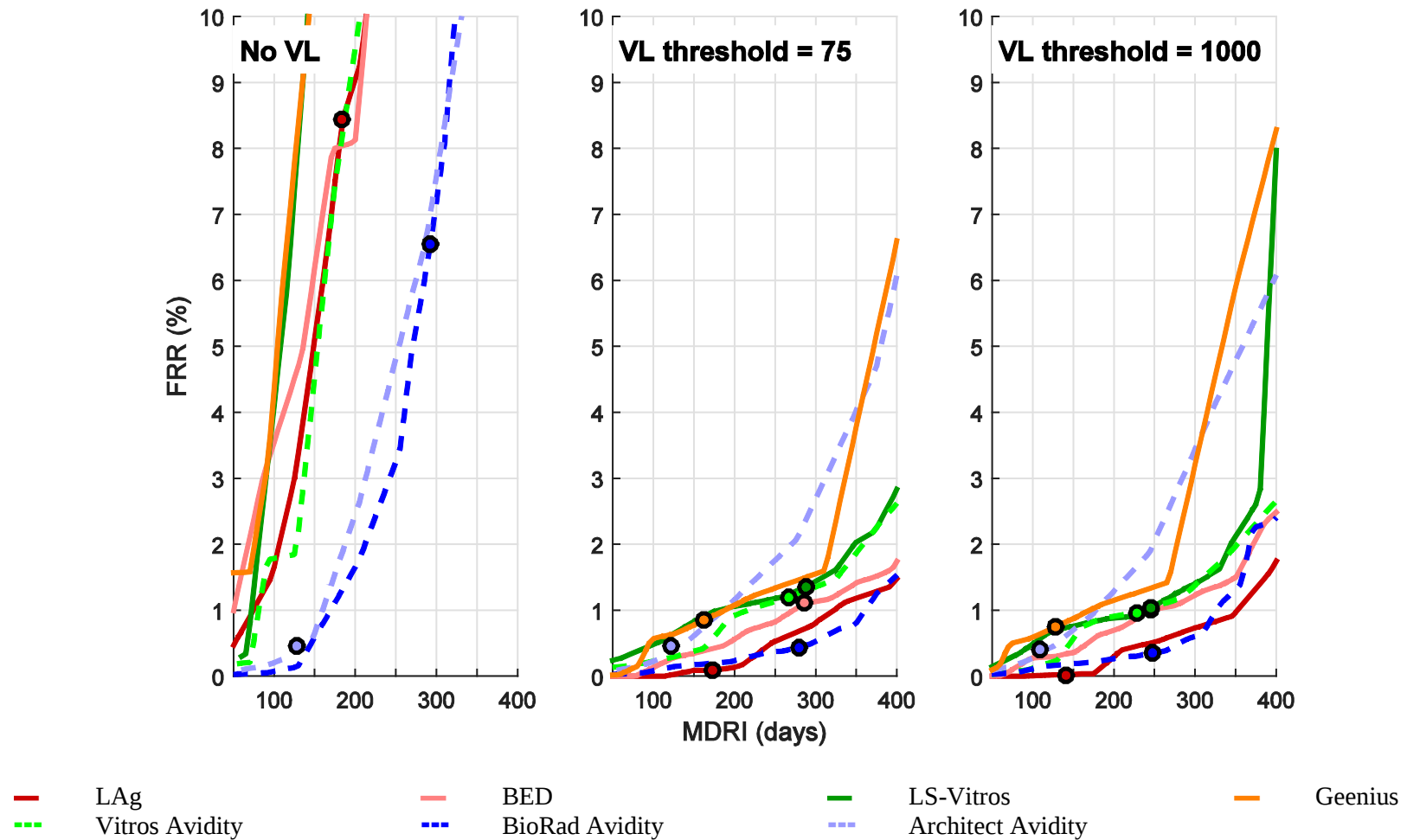
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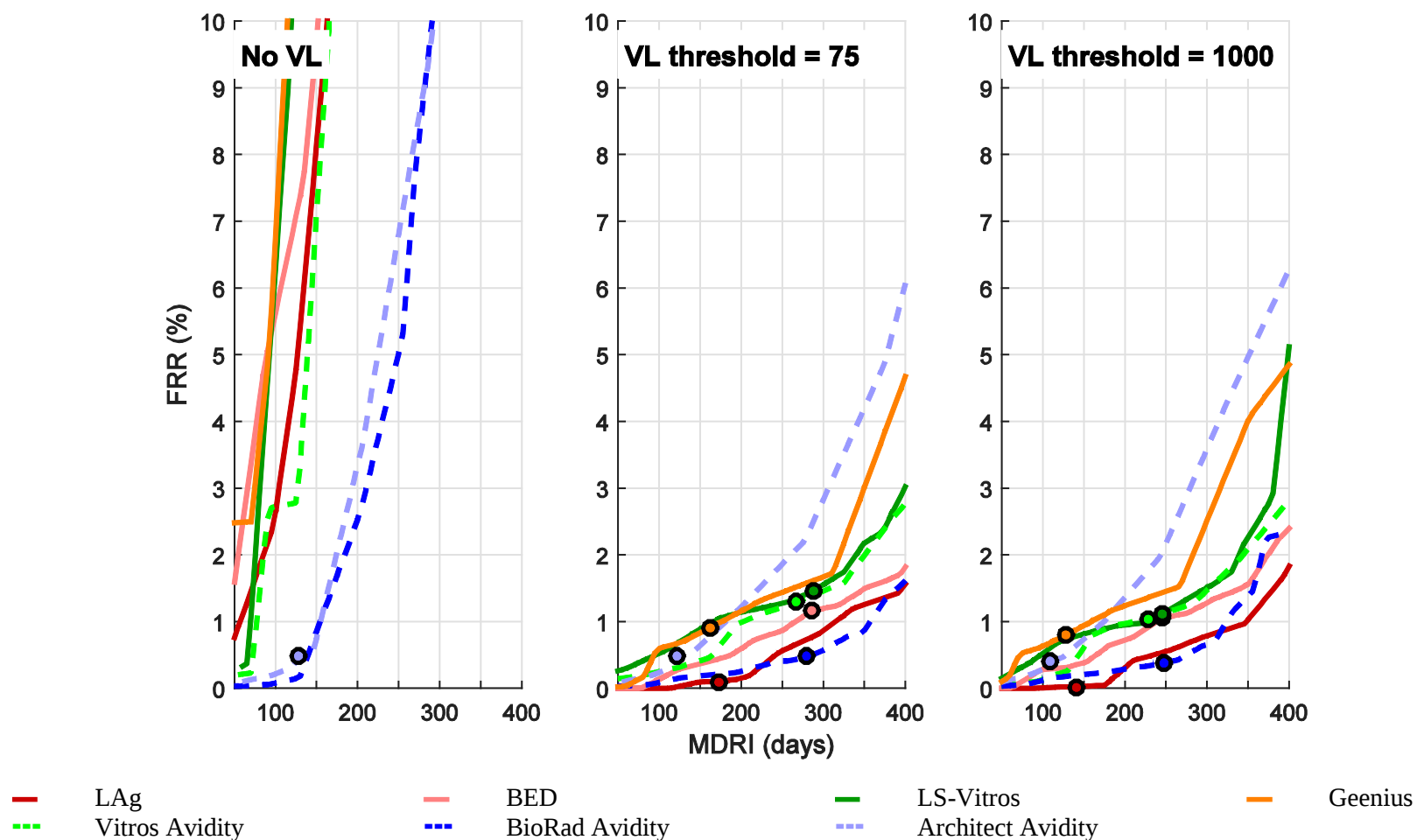
$c = 50\%$, $m = 10$



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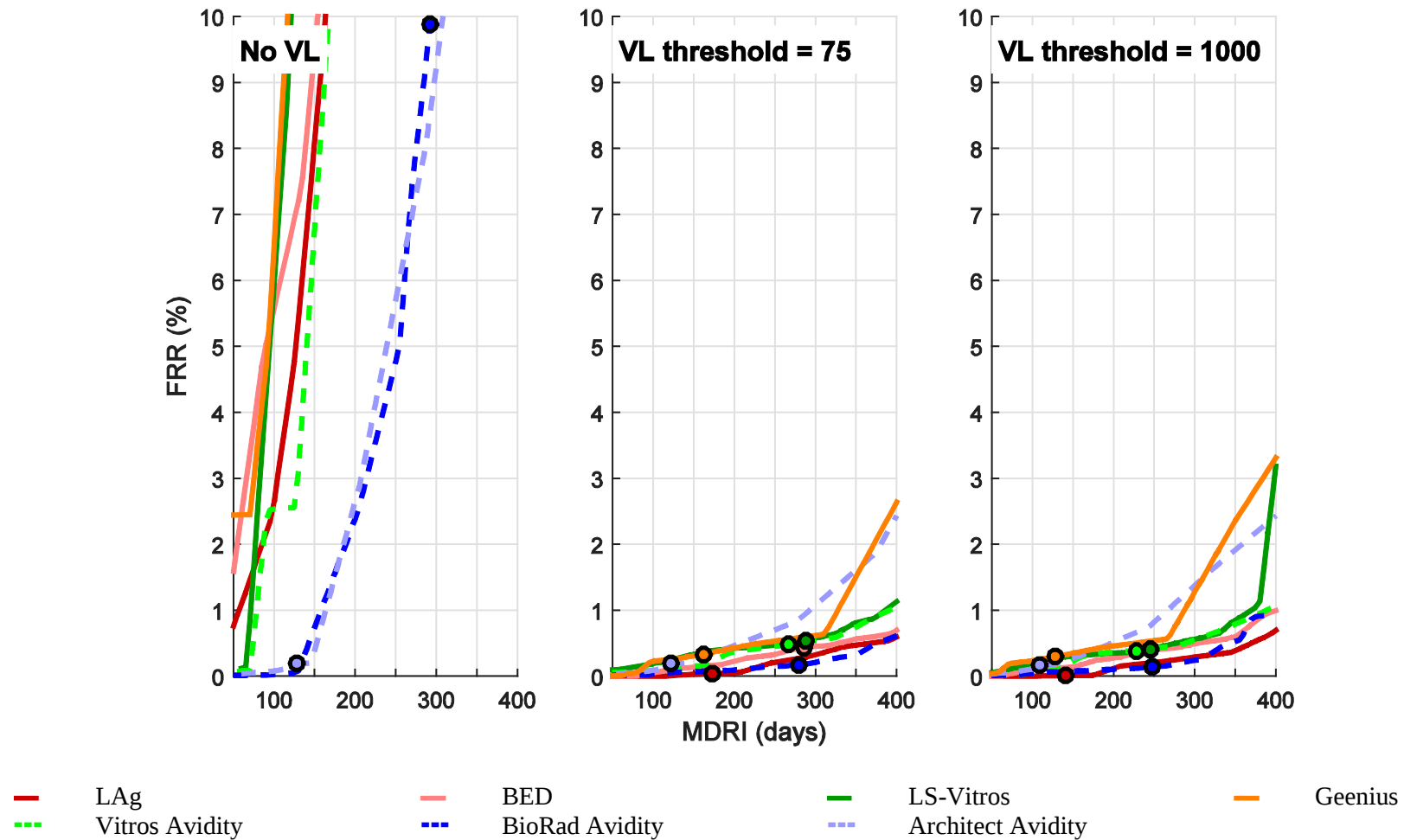
$c = 80\%$, $m = 5$



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$c = 80\%$, $m = 10$



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