MAXIMIZING THE IDEAL TIME FUNCTION IN MIRI TL VIEWER SOFTWARE

Abstract

Selecting the most viable embryo has significantly improved with the use of IVF incubators equipped with time-lapse imaging. With the increasing number of data gathered and publications released with regards to implantation potential based on morphokinetic variables, a variety of selection models, or algorithms, are being developed. The Miri TL Viewer Software is adaptive with its **Ideal Time** function fully customizable to match the clinic's requirement. One widely used predictor of embryo implantation is the cleavage timings published by ex. Meseguer et al. (2011), Campbell et al. (2013). However, despite the number of morphokinetic embryo selection models now published, such models may not be directly transferrable to another clinical setting.

Introduction

For most IVF clinics, methods of embryo evaluation mainly rely on static observation of the embryos' morphology by making observations restricted to specific times. Considering that the development of an embryo is a dynamic process, several critical stages in between observations may go unnoticed. The method often employed is subjective and varies among embryologists, which in turn, affect the outcome.

Morphokinetic Timing as an Embryo Selection-Deselection Criteria

Time-lapse observation presents an opportunity for optimizing embryo selection based on morphological grading as well as providing a novel kinetic parameter, which may further improve the accurate selection of viable embryos.[1] An increasing number of publications using time-lapse imaging report prognostic markers for embryo viability and implantation potential based on morphokinetic variables. As this technology becomes more widespread a variety of selection models or algorithms, are being developed.[2]

Meseguer et al. were among the first to publish a time-lapse model based on a quite large number of retrospective time-lapse data. The publication presented optimal values of the tx variables t2, t3, t4 and t5, combined with derivative variables of the primary tx variables called cc2 (t3-t2) and s2 (t4-t3) for embryos that did implant and embryos that did not (presented in Table 1). The four quartiles for the timing of each of the investigated variables are presented in Table 2, together with implantation percentage of embryos in each quartile. Values inside the 2nd Quartile shows the highest probability of implantation.

[1] (Meseguer, et al., 2011)
[2] (Fishel & Campbell, 2015)

Table 1. *The exact timing of embryo events analyzed from transferred implanted and not implanted embryos from Meseguer et al.*[3]

Parameter	**Implanted embryos**			**Not Implanted Embryos**		
	Mean (h)	SD (h)	n	Mean (h)	SD (h)	n
t2	25.6	2.2	61	26.7	3.8	186
t3	37.4	2.8	61	38.4	5.2	185
t4	38.2	3.01	61	40.0	5.4	182
t5	52.3	4.2	61	52.6	6.8	167
cc2	11.8	1.2	61	11.8	3.3	185
s2	0.78	0.73	61	1.77	2.83	182

Table 2. *Exact timing of the first cleavages grouped in quartiles (Q1, Q2, Q3 and Q4) from 247 transferred embryos from Meseguer et al. (2011)*

Parameter	Q1 **Limit (h)**	**Implantation (%)**	Q2 **Limit (h)**	**Implantation (%)**	Q3 **Limit (h)**	**Implantation (%)**	Q4 **Limit (h)**	**Implantation (%)**
t2	<24.3	23	24.3-25.8	32	25.8-27.9	30	>27.9	15
t3	<35.4	18	35.4-37.8	39	37.8-40.3	32	>40.3	11
t4	<36.4	23	36.4-38.9	36	38.9-41.6	31	>41.6	10
t5	<48.8	16	48.8-52.3	37	52.3-56.6	40	>56.6	14
cc2	<11.0	23	11.0-11.9	39	11.9-12.9	18	>12.9	19
s2	<0.30	36	0.30-0.76	28	0.76-1.50	20	>1.5	16

As the study performed by Meseguer et al. was among the first published on time-lapse data few references and comparisons to similar study´s was available, and the group afterwards adjusted the model as more data and comparable studies became available.

Later on, other studies into patient groups revealed a detectable change in morphokinetics between different patient groups. One we would like to emphasize here is the study by Freour et Al. 2012 between smoking and non-smoking women. Their group made a comparison of embryo morphokinetics after in vitro fertilization by ICSI (intracytoplasmic sperm injection) of embryos derived from smoking and nonsmoking women. The study revealed a statistically significant difference of the kinetics of the two groups. In summary, the embryos of smoking women developed slower than the embryos of non-smoking women. *(Table 3 shows the kinetic parameters according to female smoking status.* [4]*)*

Table 3. *Time-lapse kinetic parameters of early embryo development after ICSI in 135 couples, according to female smoking status (Freour et al.)*

Parameter	**Active Smokers, mean (SD) (n = 139 oocytes, 23 patients)**	**Nonsmokers, mean (SD) (n = 729 oocytes, 112 patients)**
t2 (h)	29.8 (7.4)	30.3 (8.3)
t3 (h)	39.91 (6.73)	38.42 (8)
t4 (h)	41.48 (8.99)	40.79 (7.49)
t5 (h)	49.97 (6.84)	48.87 (5.54)

[3] (Meseguer, et al., 2011)
[4] (Freour, Dessolle, Lammers, Lattes, & Barriere, 2012)

Another study worth highlighting is of Rubio et al. 2012 which was done as a multicenter study where the group set out to investigate implantation success of embryos that had blastomeres cleaving into three cells instead of two (also referred to as DC2-3). It is interesting to note based on retrospective analysis that embryos having blastomeres cleaving to three cells in less than 5 hours have statistically significantly lower implantation potential than embryos with a normal cell cycle length.[5] Table 4 shows that t2 on average occurred later in DC2-3 embryos than in regular cleaving embryos and t3 was occurring almost immediately after t2, making the 2nd cell cycle length very short. In non-DC2-3 embryos, cc2 lasted 12.1 hours, while for DC2-3 embryos this period was reduced to 1.8 hours.

Table 4. *Exact Timing of t2, t3, t4, and cc2 from embryos with direct cleavage (< 5 hours) from two cells (DC2-3, < 5 hours) and embryos not showing direct cleavage (non-DC2-3, ≥ 5 hours). (Rubio et al. 2012)*

	Hours after insemination			
	DC2-3 embryos (N = 715)		Non-DC2-3 embryos (N = 4,510)	
Parameter	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**
t2	29.1 ± 5.4	28.5 – 29.8	26.8 ± 3.4	26.7 – 26.9
t3	30.9 ± 5.4	30.3 – 31.5	38.9 ± 4.3	38.8 – 39.0
t4	38.8 ± 7.0	37.9 – 39.6	41.1 ± 6.0	40.9 – 41.3
cc2	1.75 ± 1.06	1.63 – 1.88	12.1 ± 2.2	12.1 – 12.2

Another study by Campbell et al. 2013 and 2014 focuses on two morphokinetic variables **tSB** (time from insemination to the start of blastulation) and **tB** (time from insemination to the formation of a full blastocyst) to evaluate the ploidy status of the embryo. The study compared ploidy status (from PGS) with time-lapse data.

From only two variables they were able to create an *Aneuploidy risk classification model* which is summarized in Table 5.[6] (For more information see Campbell et at. 2013)

Table 5. *The Three-Class Aneuploidy Risk Model based on trophectoderm biopsy data (Campbell et al. 2013)*

Risk Class	**Definition**	
	tB (hpi)	**tSB (hpi)**
Low Risk	< 122.9	< 96.2
Medium Risk	<122.9	≥ 96.2
High Risk	≥122.9	-

[5] (Rubio, et al., 2012)
[6] (Campbell, Fishel, & Laegdsmand, 2013)

Miri TL Viewer Software: Ideal Time Tool

The Miri TL Viewer Software has an **Ideal Time function** in which the clinic can fully customize event timings according to their established data. All parameters such as the ideal time events can be changed in the software by going to the Annotation Settings menu to match the clinic's requirement as shown in Figure 1. An upper and lower limit can be set to make an easy visual evaluation of the morphokinetics in the "timeline view" (figure a) and on the "deviation bar" (figure b) view (both found under the *Summary* button in the annotation page)

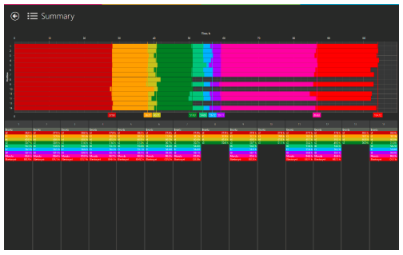

Figure a

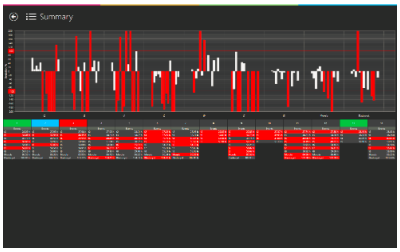

Figure b

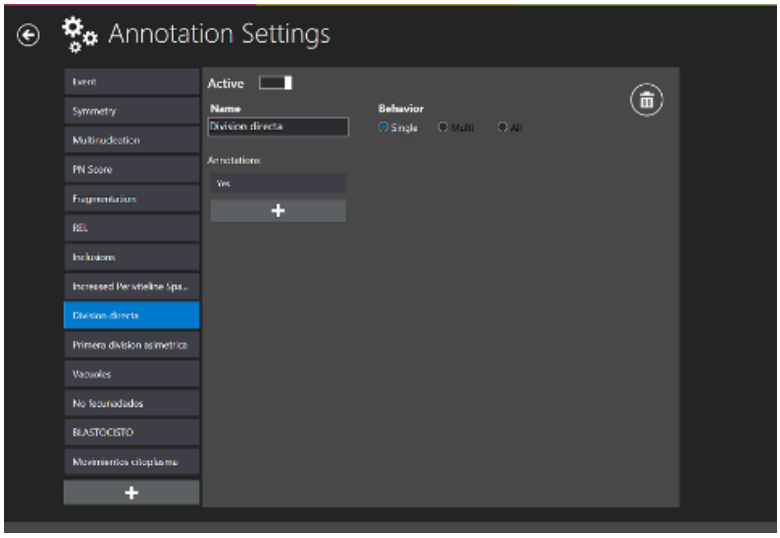

Figure 1. *Miri TL Viewer Software Annotation Settings for the Ideal Time function*

The Ideal Time function, when selected, will show a circular colored band on the outside of the annotated events in the annotation page when an embryo has been chosen (by left-clicking it with the mouse). Visually by comparing the actual cleavage time to the ideal cleavage time provides some immediate reference to the embryologists annotating the embryo. As shown in Figure 2, the colored bands outside the ring and the annotations on the left for specific time events has the same color. *(The selection of the color can be changed by customizing it in the Annotation Setting.)*

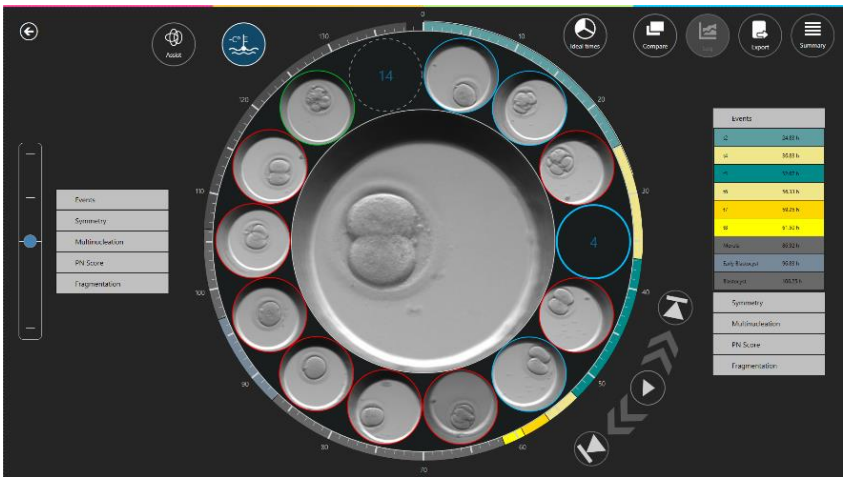

Figure 2. ***Ideal Time Function,*** *when enabled shows a colored band on the outside of the annotated events*

Conclusion

Several selection models based on morphokinetics has, and are now, being published throughout the community, we would like to emphasize, though, that such models may not be directly transferrable to another clinical setting as confounding factors may differ between different clinical setups.[7] Yalçınkaya, et al. established that each IVF laboratory is unique based on its practice. Therefore, we would like to suggest that each IVF laboratory in time should determine its own embryo selection criteria based on their own clinically gathered data.[8]

[7] (Fishel & Campbell, 2015)
[8] (Yalçınkaya, et al., 2014)

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